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Vol. 10 OCTOBER, 1935 No. 7

THE AMERICAN HEART JOURNAL

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A JOURNAL FOR THE STUDY OF THE CIRCULATION

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The American Heart Journal

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The American Heart Journal

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Original Communications

THE PRODUCTION OF A COLLATERAL CIRCULATION TO THE HEART

I. AN EXPERIMENTAL STUDY*†‡

CLAUDE S. BECK, M.D., AND V. L. TICHY, M.D.
CLEVELAND, OHIO

IT IS a perversity of nature that the most important muscular structure in the body is the most defenseless. If the blood supply to an extremity is cut off by an obstruction to a major artery, a collateral circulation to the extremity usually develops, and function is restored. If the blood supply to the heart is cut off by an obstruction to a major artery, the heart may come to a complete and permanent standstill, and little or no opportunity is afforded for a collateral circulation to develop. The appalling incidence of sudden death from heart failure in our adult population attests to the destructive nature of coronary disease.

Man's anatomical pattern provides the heart with two almost frictionless surfaces which constantly glide over each other. The only direct continuity of the heart with the rest of the body is through the walls of the great vessels, the fat, the nerves, and the lymphatics which form an anchorage for the heart, so to speak, at its base. While the heart is in direct contact with other structures over its entire surface, it has a minimum amount of direct continuity with such adjacent structures. Unwittingly, nature to a marked degree has deprived the heart of a most important compensatory property, namely, that of developing an adequate collateral blood supply to meet an emergency, to preserve life during the first moments, hours, days, and weeks after a serious coronary

*From the Laboratory of Surgical Research of the Western Reserve University School of Medicine and the Lakeside Hospital.

†Aided by a grant from the Josiah Macy, Jr., Foundation.

‡Read at the meeting of the Cleveland Section of the Society of Experimental Biology and Medicine, December 14, 1934. [Beck, C. S., Tichy, V. L., and Moritz, A. R.: Production of a Collateral Circulation to the Heart (Preliminary Report), Proc. Soc. Exper. Biol. and Med. 32: 759, 1935.]

accident. If life is preserved over a sufficiently long period of time, the process of coronary occlusion can go on to completion.[1] In other words, complete closure of the coronary ostia at the aorta is compatible with life. In these cases the myocardium draws from other sources for its blood supply. The substitution of another source of blood supply for the normal source of blood supply must be done slowly. It can be done, but the number of times that nature has succeeded in making this substitution is excessively small. At some place along the way life is snuffed out like a candle flame.

Under normal conditions the heart has three sources from which it can receive a supply of blood: the coronary arteries, the thebesian vessels, and the extracardiac anastomoses between the coronary system and the blood vessels in the fat and other tissues at the base of the heart. The tissues at the base of the heart normally are not richly vascularized, but communications between the coronary system and the vessels in these tissues have been demonstrated.[2] Blood vessels have been demonstrated also in adhesions between heart and pericardium.[3] These extracardiac anastomoses were demonstrated by the injection of lampblack into the coronary system. That such blood vessels exist in adhesions to the human heart was confirmed by direct observation at operation (C. S. Beck, Nov. 10, 1934). In this instance an adhesion extended from the base of the left ventricle to the parietal pericardium. When the adhesion was cut, active bleeding occurred from each end of the transected tissue. The bleeding appeared to be more brisk from the cardiac end than from the pericardial end. This is the first direct observation of the functional nature of such blood vessels in man.*

Our interest in the production of a collateral vascular bed to the heart was an outgrowth of a discussion that Dr. Alan R. Moritz had with the senior author of this paper (C. S. Beck) toward the close of 1931. He directed attention to the presence of blood vessels in pericardial adhesions in cases without any coronary occlusion and also in cases with coronary occlusion. He referred to the case reported by Thorel[4] in 1903—in a patient who had pericardial adhesions and complete obliteration of both major coronary arteries. It was suggested by Thorel and emphasized by Moritz that these adhesions provided a blood supply to the heart. On the basis of this information it became our intention to produce experimentally a new vascular bed to the heart. The first experiments with this purpose in mind were done by Beck in February, 1932. Dr. Moritz followed the work with interest and gave us valuable suggestions concerning the injection and study of the specimens.†

*We observed the vascular nature of cardiopericardial adhesions in experimental animals several years ago in our studies of chronic cardiac compression.

† We also desire to thank Dr. Carl Wiggers, Dr. Carl Lenhart, Dr. Howard T. Karsner, and Dr. Joseph T. Wearn for suggestions and interest in the work, and also the various internes in the Lakeside Hospital for assistance in many of the operations.

METHOD

The problem of producing a new blood supply to the heart resolved itself into two components. One was to make available a satisfactory vascular bed for the heart. The other was to produce the stimulus which would bring about continuity between the cardiac and extracardiac vascular beds. The work progressed largely by virtue of the trial and error method. The operative procedure underwent almost constant evolution.

The available bed for vascularization of the myocardium consists of the pericardium, pericardial fat, mediastinal tissues, pleura, diaphragm, substernal muscles, the musculature of the thoracic wall, and the omentum. In these experiments the pericardium, the pericardial fat, and the mediastinal tissues were utilized for the vascular bed (Figs. 1 and 2). A series of experiments is now being carried out in which adjacent muscles are being utilized for the source of blood supply. We are also carrying out experiments in which the omentum is brought to the heart through an opening in the diaphragm. Direct continuity between the vascular bed and the heart was established by the production of adhesions. The methods of producing adhesions were by incision of myocardium and suture of pericardium into the wound or by removal of epicardium and endothelial lining of the pericardium. Sandpaper, emery paper and finally special burrs were used for this purpose. The stimulus necessary to bring about vascular continuity between the extracardiac and cardiac beds was a reduced or subnormal pressure in the coronary bed.* The pressure was reduced by occluding the coronary arteries. The flow through the coronary arteries can be reduced either slowly by successive operations or by complete ligation in one stage. The obstruction can be applied to major coronary trunks or anywhere toward the peripheral branches. Obviously the most desirable form of coronary obstruction is a slowly progressive obstruction going on to complete obstruction. With this purpose in mind, bands of periosteum were wound around the coronary arteries at their origins from the aorta. The most satisfactory method of producing gradual occlusion of a major coronary artery was that of repeated operation. We used clips that we made from sheet silver. These clips were shaped as illustrated (Fig. 3) and were progressively clamped together at successive stages. In order to locate the clip at operation a piece of silk or wire was looped around the artery close to the clip, and the ends were left long so that they could be found later at operation. If at a subsequent operation the clip could not be dissected free of scar tissue, complete occlusion of the artery was effected by means of the silk or wire loop.

*Perhaps the variation in mediastinal pressures accompanying respiration can augment the development of collateral vessels to the heart. The alternate application of positive and negative pressure to an extremity can augment the blood supply to the extremity. Perhaps active exercise of the animal would have been valuable in these experiments.

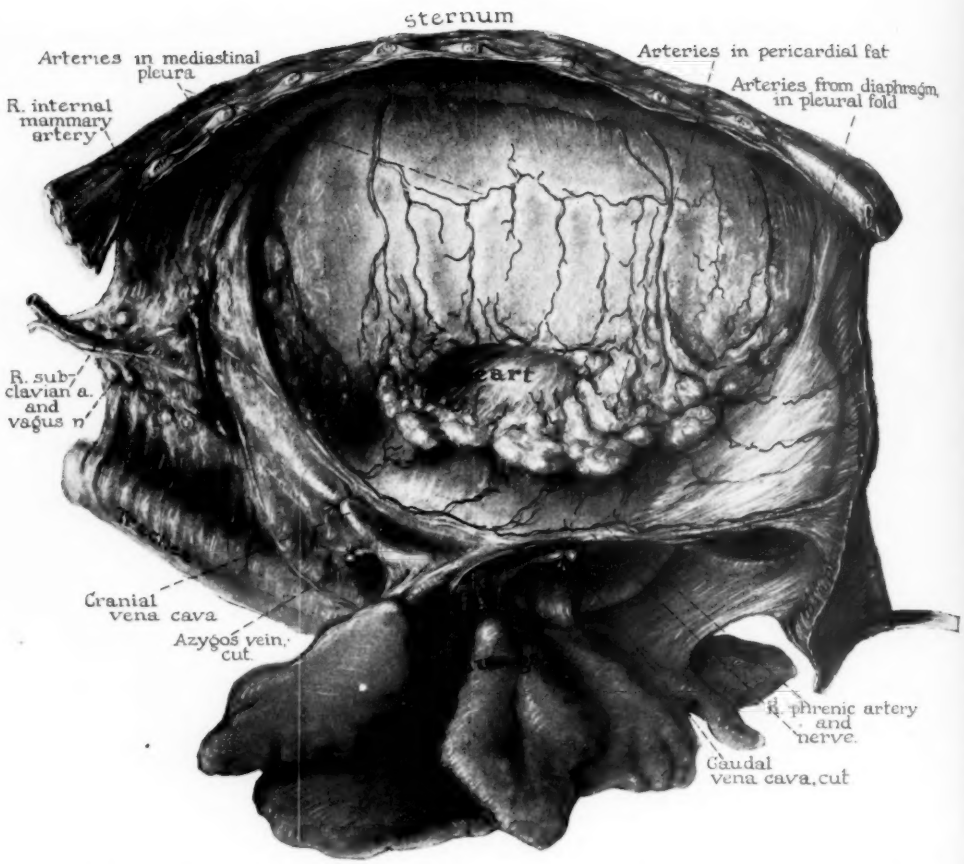

Fig. 1.—The available vascular bed to the heart in the dog as seen from the right side of the chest. This bed consists of the pericardial fat, the parietal pericardium, and the mediastinal tissues. The internal mammary arteries and the substernal muscles can also be transplanted to the surface of the heart.

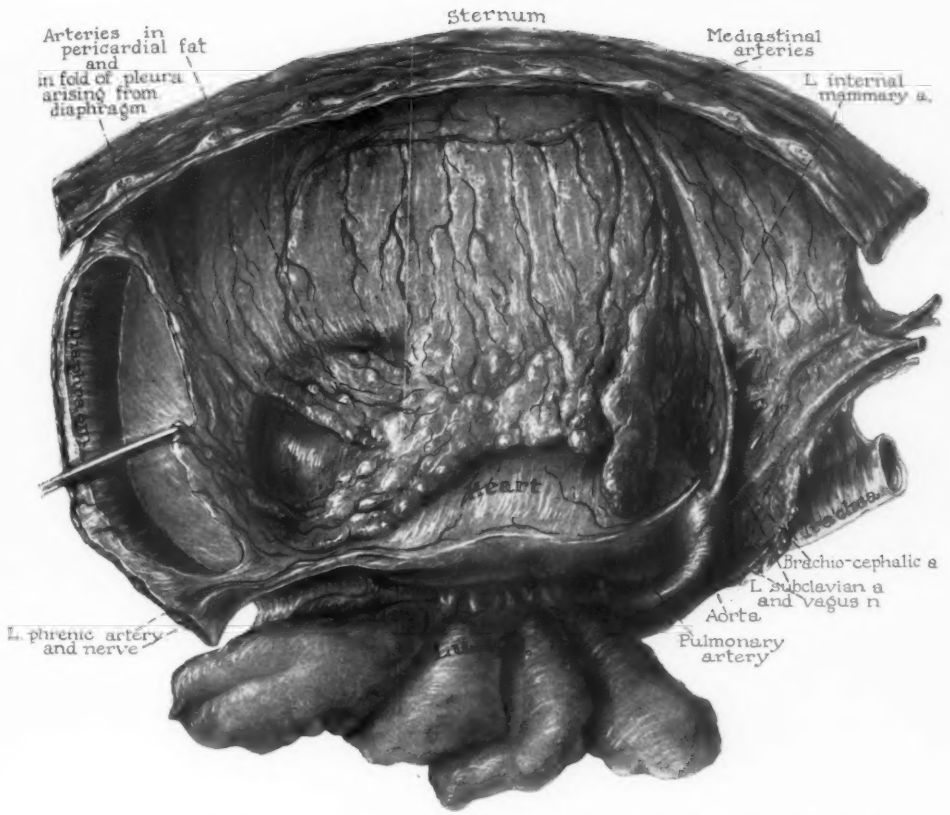

Fig. 2.—The available vascular bed in the dog as viewed from the left side of the chest.

The anastomoses between the extracardiac vascular bed and the heart were determined by the injection of ferric ferrocyanide. The dye was injected into the collateral bed from the aorta, the ostia of the coronary arteries and the thebesian channels being excluded from the injection system (Fig. 4). The usual order of procedure was as follows:

The dog was anesthetized with ether through an intratracheal tube. Mechanical respiration was used. The right carotid artery was connected to a flask. The left carotid artery was connected to a mercury manometer. The inferior vena cava was isolated at its junction with the auricle. A T-tube was placed in this vessel; the long arm of the tube was clamped, and blood was allowed to run through the short arm into the auricle. The superior vena cava and the azygos vein were isolated (but not ligated) close to the auricle. The clamp was removed from the long

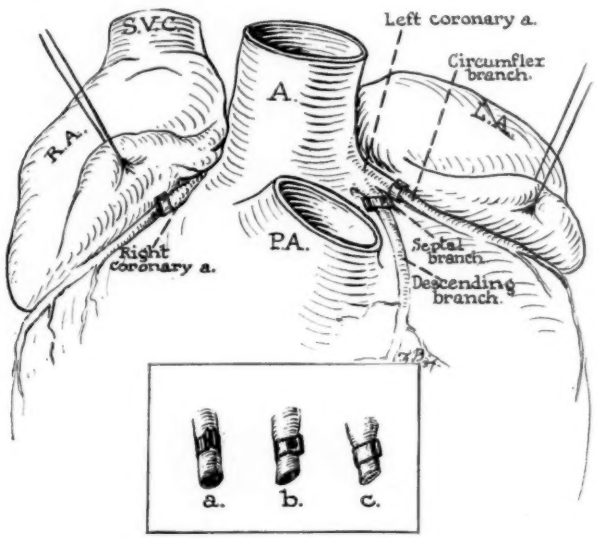

Fig. 3.—The usual site of producing occlusion of the coronary arteries by bands or clips, made from sheet silver. The clips are compressed in successive stages as indicated in *a*, *b*, and *c* of the inset.

arm of the T-tube in the inferior vena cava, and the animal was bled. Two liters of normal saline at a temperature of 38° C. was washed through the circulation by way of the flask connected to the right carotid artery. The superior vena cava and the azygos vein were then ligated close to the auricle. The inferior vena cava was clamped between auricle and cannula. The right auricle was incised so that we were certain that fluid could not enter the heart. The aorta was securely clamped close to its origin, and the aorta was cut across between clamp and heart so that fluid could not enter the ostia of the coronary arteries. Following this, 0.4 per cent of aqueous solution of ferric ferrocyanide at normal body temperature was injected under gravity pressure of about 180 cm. The injection was continued for 30 minutes. The pressure

in the left carotid artery usually varied from 100 to 120 mm. Hg during the injection. The dye was allowed to escape from the inferior vena cava during the injection. Usually about eight liters of the dye were used. Usually the heart continued to beat up to, and even for a few moments after, the injection of dye was started. With the heart segre-

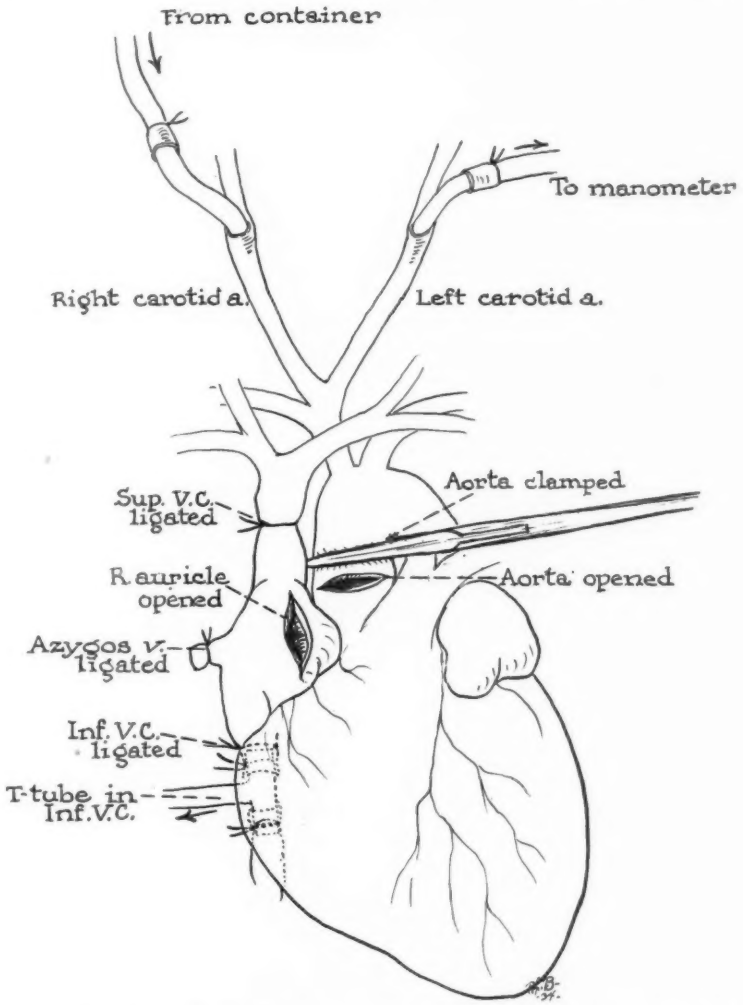

Fig. 4.—Method of injection of heart through extracardiac anastomoses. The ostia of the coronary arteries and of the thebesian channels are isolated from the injection system. Dye can enter these structures only through anastomoses with the extracardiac vessels.

gated from the circulation (except for the extracardiac collateral vascular bed) and with the right auricle and aorta opened, it was considered to be impossible for any of the dye to enter the myocardium through the ostia of the coronary arteries or through the thebesian vessels. The heart was not touched or massaged in any way while the injection was in

progress. Under these conditions the myocardium could be injected only through the extracardiac anastomoses. An alternative method of injection, which we rarely used, consisted of cannulating the coronary arteries and injecting the coronary system and then determining the spread of the injection into the extracardiac tissues.

A number of attempts were made to carry out the injection and at the same time have the heart receive and expel its usual quota of blood. These experiments were not successful and will not be recorded.

EXPERIMENTS

This report is based upon the study of 103 dogs in which one or more operations were carried out to produce a collateral circulation to the heart, and upon sixteen dogs in which various methods were used for injection of the heart through the extracardiac anastomoses. One hundred and sixty-five operations were performed on the 103 dogs. On some of the dogs as many as four operations were performed. Many of the operations consumed three or four hours, and some of them were something of an achievement in technical surgery.

The following protocols are given as illustrations of the various types of experiment that were done.

Protocol 1.—Dog No. 33-131. This was a normal dog. Injection of the extracardiac anastomoses was carried out. The mediastinal tissues, pericardial fat, and parietal pericardium were diffusely stained. The right and left coronary arteries were filled with dye. A trace of dye was seen in each auricle near the entrance of the great veins. On cross-section of the heart the only dye seen was in the main trunks of the coronary arteries (Fig. 5). There was no dye in the myocardium either grossly or microscopically.

Protocol 2.—Dog No. 33-146. This was a normal dog. Injection of the extracardiac anastomoses was carried out. The mediastinal tissues, pericardial fat, and parietal pericardium were diffusely stained. The right and left coronary arteries together with their superficial branches contained dye. The fat at the base of the aorta was stained and the auricles were faintly blue; the left auricle was stained a little more than the right. Cross-section showed dye in the larger branches of the coronary arteries to a greater extent than in the preceding specimen (Fig. 6). Microscopically the left auricular appendage contained arteries filled with dye, but there was no capillary injection. Extensive but focal capillary injection was present in a section of the right ventricle limited to the narrow zone of myocardium that extends out for a short distance in the wall of the pulmonary vein. Several fairly large arteries (one measured 150 micra in outside diameter) extended between the heart and the extracardiac structures.

Protocol 3.—Dog No. 33-141. This was a normal dog. Injection of the extracardiac anastomoses was carried out. The pericardial fat and the parietal pericardium were well injected. Dye contained in vessels could be seen entering the auricles and the conus arteriosus with some extension into the ventricular myocardium at the base of the heart. The largest anastomotic vessels were the vasa vasorum of the pulmonary artery and of the aorta. The adventitial fat around the great vessels was well injected. The surface of the heart showed some diffuse injection which was most marked just below the atrioventricular sulcus. The superficial

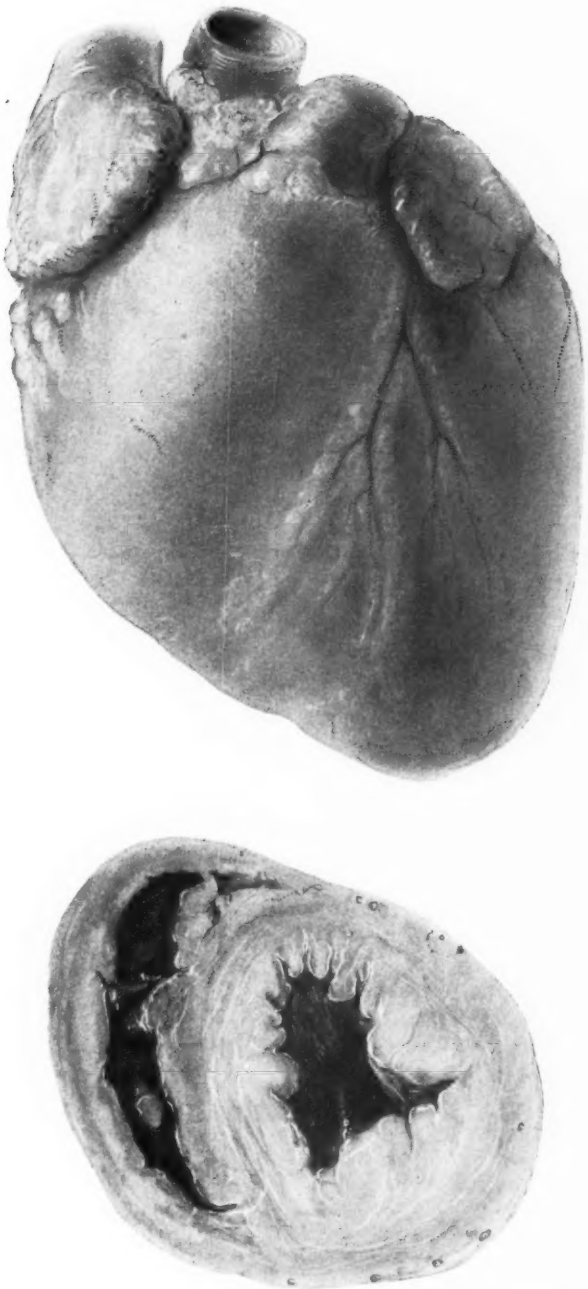

Fig. 5.—Protocol 1 (Dog No. 33-131). Normal heart after injection with dye.

branches of the coronary arteries were filled with dye. On cross-section some dye was present in the superficial portion of the myocardium, especially in the left ventricle. The walls of both auricles were fairly diffusely injected. There was no diffuse staining of the myocardium grossly (Fig. 7). Microscopically all the large and most of the small arteries in a section of the left auricular appendage contained dye. This section also showed focal, scanty capillary injection. A section of the left ventricle showed that all the large vessels and many of the small vessels contained dye. This section also showed some focal, scanty capillary injection. The section showed questionable fibrosis. There was no infarction. A section of the right ventricle showed that some of the large and very few of the small arteries contained dye. The epicardium and the subepicardial portion of the myocardium showed slight focal capillary injection.

These specimens represent the slightest and the greatest degree of injection through the extracardiac anastomoses that we found in our series of normal dogs.

Protocol 4.—Dog No. 34-18. Feb. 27, 1934: A loop of wire and a silver clip were placed around the two major branches of the left coronary artery below its bifurcation. The circumflex branch was constricted about four-tenths. The right coronary artery was constricted about one-half of its normal cross-section. Throughout this operation great beads of clear fluid were observed to form on the surface of the heart.* Epicardiectomy† was done with our special burrs, and the endothelial lining of parietal pericardium was roughened with these burrs. Death occurred March 3, 1934, from cardiac failure. The degree of occlusion of the coronary arteries was too great.

Protocol 5.—Dog No. 33-30. April 18, 1933: A loop of silk and a loop of periosteum were placed around each major branch of the left coronary artery just below its bifurcation and also around the right coronary artery close to its origin from the aorta. These vessels were not constricted by these loops of silk and periosteum. The strand of periosteum was taken from a rib and was about 3 mm. in diameter. The epicardium and the inner surface of the parietal pericardium were scraped with a scalpel. The pericardium was sutured to the heart. Dec. 10, 1934: The animal was killed, and the heart was injected. Generalized adhesions to the pericardium and pericardial fat were present. These tissues were deeply injected. When the myocardium was cut across, it was found that the dye had not penetrated the myocardium. The coronary arteries showed no constriction. Our interpretation of this experiment was that in the absence of partial occlusion of the coronary arteries vascularization of the myocardium from the adherent pericardium did not take place. In other words, there was no unusual need for additional blood during life, and no additional vascularization of the myocardium took place (see Protocol 15).

Protocol 6.—Dog No. 33-62, weight 13.6 kg. June 14, 1933: The left coronary artery was isolated at its bifurcation. A loop of silver wire was placed around the descending and the circumflex arteries. A silver clip was placed around the circumflex branch occluding its lumen to a moderate degree. A silver clip was placed on the

*This is the second observation of drops of fluid forming from the heart in an experience of over a thousand experimental operations on the heart (C. S. B.). Fluid formed at one point like a bead of perspiration every few seconds.

†In so far as we know this is the first time that the term epicardiectomy has been used and in so far as we know this is the first time this operation has been done. In some animals the epicardium came away in large sheets; in others it came away in shreds. The epicardium is quite tough and undoubtedly gives considerable support to the myocardium. It is of considerable importance as a surgical structure. It helps to prevent sutures from tearing out of the heart and in this respect is not unlike the submucosa of the small intestine.

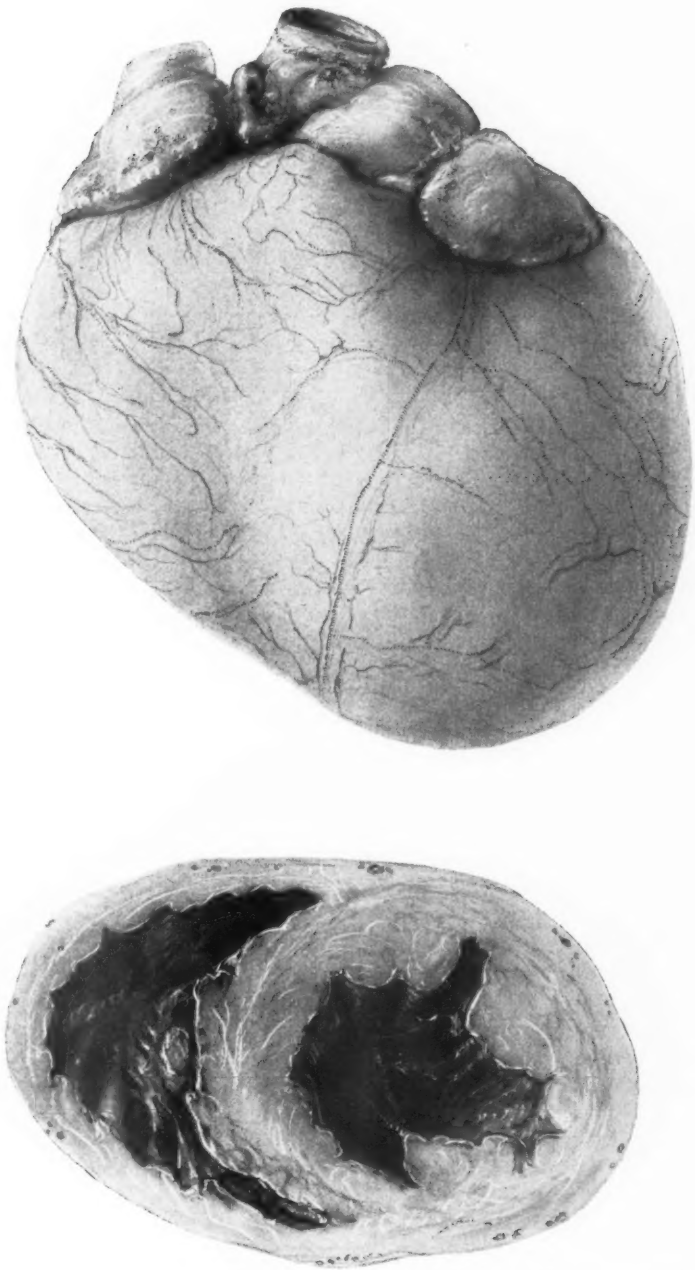

Fig. 6.—Protocol 2 (Dog No. 33-146). Normal heart after injection with dye.

descending branch occluding its lumen to a somewhat greater degree. A loop of wire and a silver clip were placed around the right coronary artery where the vessel lies beneath the right auricle. This vessel was occluded partially. The epicardium was roughened with a burr and in certain areas was entirely removed. The parietal pericardium was roughened and torn with the burr. The animal made an excellent recovery. Oct. 2, 1933: Reoperation—The silver wires were brittle and were easily broken. The clip on the right coronary artery was located. It was crushed and the right coronary artery was completely occluded. The silver wires on the branches of the left coronary artery were isolated. The wire on the circumflex branch was tightened producing total occlusion. Since the heart could not stand total occlusion of the circumflex artery, the tension on the artery was released. Tension applied to the wire on the descending artery was tolerated, and the wire was twisted tightly to occlude this vessel completely. Oct. 6, 1933: The animal appeared to be in excellent condition. He was active and playful. The electrocardiogram showed high take-off of the T-wave in Leads I and II. Sept. 28, 1934: (Weight 14.5 kg.) The dog was killed for study of the specimen. The injection was carried out as already outlined. Grossly the adherent fat and pericardium, as well as the entire muscle, were diffusely injected (Fig. 8). There was a small cicatrix (about 12 mm. in diameter) in the lateral wall of the right ventricle which was judged to represent a healed infarct. Microscopically there was extensive capillary injection in sections taken from six different portions of the heart. Examination of the left coronary artery showed the descending branch to be completely occluded, the circumflex branch to be patent only to a fine probe, measuring about 2 mm. in circumference, and the septal branch to be intact. The septal branch measured 3.5 mm. in circumference. The right coronary artery was completely occluded about 1 cm. from the aorta. There were six very fine twigs that could be identified coming off the right coronary artery between the clip and its ostium in the aorta. We estimated that the total cross-sectional area of the coronary arterial system was reduced about 85 per cent.

Protocol 7.—Dog. No. 32-51, weight 18.5 kg. Mar. 23, 1932: The pericardium was sutured to the left side of the thoracic wall for a purpose other than for these experiments. Mar. 21, 1933: The attachment to the thoracic wall was incised, and the heart was exposed. Superficial incisions were made over the surface of the ventricles with a scalpel. The pericardium was sutured to the heart and also to the thoracic wall. Sept. 1, 1933: A silver clip and a wire loop were placed around each major branch of the left coronary artery just below its bifurcation. The heart stopped. The wire was removed, but clips were left in place. Epinephrine and massage were used, and the heart started to beat. Some obstruction was given to each major branch of the left coronary artery. The heart action was irregular. The right coronary artery was not isolated. Feb. 17, 1934: An attempt was made to isolate the right coronary artery. Several mass ligatures were placed in what was considered the anatomical location of the right coronary artery. Scar tissue obscured its location. Oct. 2, 1934: The animal was in good health. It was active and well nourished and weighed 17.0 kg. Two and one-half years had elapsed since the first operation. The animal was killed for study. The heart was injected, and the specimen was cut and examined by Dr. Moritz, Dr. Wiggers, Dr. Lenhart, and Dr. Karsner. The measurements as given by Dr. Moritz were as follows: The right coronary artery for a distance of 3 cm. from its ostium had a circumference of 4 mm. There was no obstruction to this vessel. The left coronary artery just below its ostium and above its bifurcation had a circumference of 9 mm. The ramus descendens had a circumference of 3 mm. at the site of obstruction and 6 mm. below the silver clip. The artery above the clip was narrowed. The septal branch came off above the obstruction. It was a very small vessel. The circumflex artery was

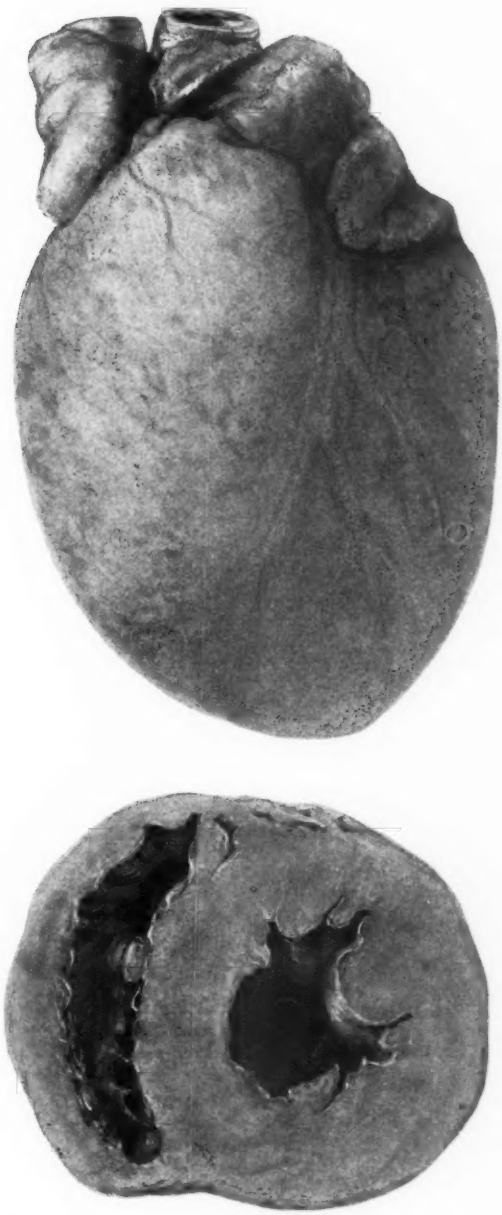

Fig. 7.—Protocol 3 (Dog No. 33-141). Normal heart after injection with dye. This specimen shows the greatest amount of injection through the extracardiac anastomoses found in our series of sixteen normal specimens.

reduced to a circumference of 1.5 mm. at the site of the obstruction. Below the clip it measured 6.5 mm. in circumference. According to these measurements the cross-section of the ramus descendens was reduced about 75 per cent and the cross-section of the ramus circumflexus was reduced about 95 per cent. The right coronary artery was relatively a small artery, and it appeared that an extracoronary collateral circulation was established in preference to compensation by enlargement of the right coronary artery There was complete fibrous obliteration of the pericardial cavity. There was diffuse injection of the myocardium although there was some variation in intensity of the dye. The least injected portion was the anterior papillary muscle in the left ventricle. Although there was no infarction, there was considerable focal myocardial fibrosis. This scarring was most extensive in the posterior portion of the interventricular septum and left ventricle. Microscopically the capillary injection was extensive (Fig. 9), and sections taken from six different portions of both ventricles failed to disclose differences in distribution of dye described grossly. The amount of Prussian blue in skeletal muscle was 89 mg. per 100 gm. of muscle and the amount of dye in the cardiac muscle was 84.5 mg. per 100 gm. of heart.

Protocol 8.—Dog No. 33-139. Dec. 12, 1933: The left coronary artery was isolated at its bifurcation, and a loop of wire and a silver clip were placed around each major trunk. Some obstruction was given to each artery. The right coronary artery was isolated, and its lumen reduced about one-half. The epicardium and parietal pericardium were roughened with a burr. June 28, 1934: An attempt was made to reduce further the lumen of one branch of the left coronary artery. The clips and wire loops were covered with scar tissue, and accurate isolation was impossible. Oct. 2, 1934: The animal was killed, and the specimen was injected (Fig. 10). The cross-sectional area of the right coronary artery was reduced about 25 per cent. The left coronary artery showed slight reduction in lumen by the clips. The cardiac muscle contained 22 mg. of Prussian blue per 100 gm. of muscle, and the skeletal muscle contained 107 mg. of dye per 100 gm. of muscle. The pericardial cavity was obliterated, but parietal pericardium could be stripped from the heart. The adhesions were not very dense. There was some diffuse injection of both auricles. There was slight injection of the ventricles, more marked in the right than in the left. There was no sign of myocardial fibrosis or infarction. Microscopical sections showed some diffuse injection of large and small arteries of both ventricles, more marked in the right than in the left. There was very little capillary injection in the inner half of the left ventricle. The adhesions to the myocardium were richly vascularized by small vessels containing dye. There was no fibrosis or infarction in the sections.

Protocol 9.—Dog No. 34-4. Jan. 15, 1934: The left coronary artery was isolated and a wire loop and a silver clip were placed around each major branch. The reduction in lumen was estimated to be one-half. Similarly the right coronary artery was constricted about one-half by a silver clip. July 11, 1934: The clip on the descending branch of the left coronary artery was isolated and the lumen was further reduced. Oct. 3, 1934: The animal was killed, and the heart was injected. There was apparently complete injection of the parietal pericardium. The pericardial cavity was obliterated by fibrous adhesions. Both ventricles showed diffuse but incomplete injection with dye. The degree of injection was greater in the anterior portion of the left ventricle extending from base to apex. This area was supplied by the ramus descendens of the left coronary artery. There was no gross or microscopical evidence of fibrosis or infarction. Microscopically many large dye-containing vessels were present in the myocardial adhesions. The sections of myocardium taken for examination showed diffuse capillary injection with dye. The ramus descendens was obstructed more than the ramus circumflexus. The circumference of the ramus descendens at the clip was 5 mm., below the clip 7 mm. The

Fig. 8.—Protocol 6 (Dog No. 33-62). Extensive injection of the myocardium through the vascular bed established by operation. New blood vessels can be seen.

circumference of the ramus circumflexus at the clip was 3.5 mm., below the clip 5 mm. The right coronary artery had a circumference of 4 mm. at the clip and 5 mm. below the clip. The degree and distribution of the injection in this experiment, as well as in other experiments, seemed to vary with the degree of obstruction to the various coronary arteries; that is, the greater the obstruction, the greater the injection.

Protocol 10.—Dog No. 32-106. May 6, 1932: Several branches of the left coronary artery were ligated over the apex of the left ventricle. The areas of myocardium supplied by these vessels became discolored after ligation and appeared dark and cyanotic. Sutures were placed between pericardium and heart.

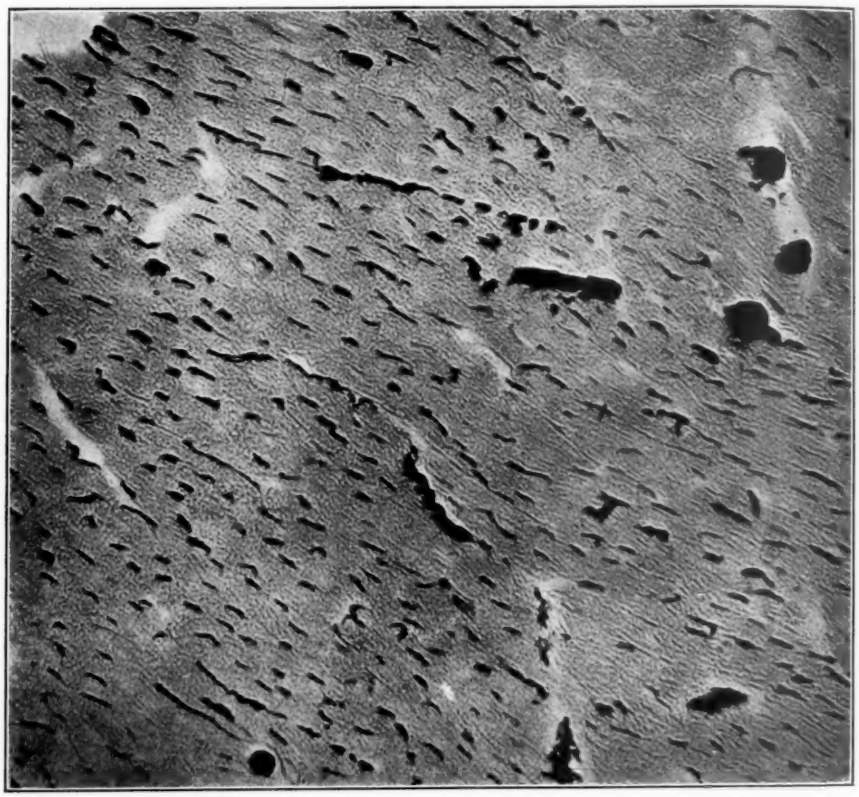

Fig. 9.—Protocol 7 (Dog No. 32-51). Wall of left ventricle, stained with eosin only, showing extensive capillary injection. The injection mass entered the myocardium through the vascularized pericardial adhesions. The capillaries are filled with dye and appear black (magnification ×210).

Mar. 13, 1933: Several mass sutures were placed in each ventricle to produce peripheral occlusion of the coronary arteries. Apr. 24, 1933: A loop of periosteum was placed around each major branch of the left coronary artery just below its bifurcation. June 10, 1933: Three mass ligatures were placed with the purpose of producing total occlusion of the ramus descendens high in its course. The anatomical location of this artery was obscured by adhesions. Feb. 5, 1934: The animal was killed, and the specimen was injected. Scattered pericardial adhesions were present. The parietal pericardium was well injected. The epicardium showed an excellent injection with dye. The right ventricular wall showed a fairly complete

Fig. 10.—Protocol 8 (Dog No. 33-139). A slight degree of injection with dye in response to a slight degree of coronary obstruction.

injection. The interventricular septum showed a scanty injection, and the wall of the left ventricle showed a superficial injection (3-5 mm.). There was no apparent fibrosis or infarction. Capillary injection of the right ventricle was present in the more superficial portion. The large and small arteries of the right ventricle were everywhere injected. The left ventricle showed less injection than the right. One small infarct was found. The ramus descendens was completely occluded just below the bifurcation of the left coronary artery. The ramus circumflexus showed no occlusion.

Protocol 11.—Dog No. 33-16. Mar. 30, 1933: The left coronary artery was isolated at its bifurcation and a loop of periosteum was placed around each of the two major branches. The degree of constriction on the ramus descendens had to be reduced because the heart stopped. It was revived, and the loop of periosteum was again applied. The epicardium and parietal pericardium were scraped with a scalpel. Sutures were placed between pericardium and myocardium. June 1, 1933: The ramus circumflexus could not be isolated. The ramus descendens was ligated completely at its origin. An attempt to isolate the right coronary artery was not successful. Mass sutures were placed in an attempt to ligate this artery. The animal had sharp pain after operation, most probably coronary pain. Morphine was given. Mar. 13, 1934: The animal was killed and the heart was injected. The pericardium was adherent to the auricles, to the base, anterior and lateral aspects of the heart. An extensive injection of the left ventricular wall was present (Fig. 11). Slight injection of the right ventricular wall was found. The auricular walls showed slight injection. There was no gross or microscopical evidence of fibrosis or infarction. Sections including the fused pericardial surfaces showed rich vascularization of the intervening connective tissue. These vessels were uniformly filled with dye. The arteries and capillaries of the right and left ventricles and interventricular septum contained dye. The capillary injection varied in extent and was most pronounced in the superficial portion. Nowhere was complete capillary injection found. Focal fibrosis, but no infarction, was found in each ventricle. These areas of fibrosis were probably due to the sutures that were placed in the myocardium. The ramus descendens was completely obstructed. The ramus circumflexus was slightly constricted but was easily patent to a probe. The right coronary artery was slightly constricted but also admitted a probe readily.

Protocol 12.—Dog No. 33-42. May 17, 1933: The left coronary artery was isolated. A loop of silk and a silver clip were placed around the circumflex branch. The ramus descendens was unusual in that there were three separate descending arteries instead of one. A large vein crossed these arteries. The clip on the circumflex artery reduced the lumen about one-half. The epicardium and the inner surface of the pericardium were roughened with emery paper. Aug. 7, 1933: Two relatively large vessels were seen extending from the pericardial fat to the region of the internal mammary vessels. The pericardial tissues were more vascular than normal. The braided silk loop around the circumflex artery was isolated, and this artery was ligated. A silver clip and a loop of silk were placed on the right coronary artery. This artery was partially occluded. Oct. 10, 1933: The braided silk around the right coronary artery was isolated, and a knot was tied in the silk. The clip could not be found. There was good recovery. Feb. 22, 1934: The animal was killed for study; the specimen was injected. The parietal pericardium was diffusely injected. The pericardial cavity was completely obliterated. A multilocular organized abscess was found at the base of the heart to the left of the pulmonary conus. The adhesions showed a diffuse injection with dye. The superficial branches of the coronary arteries were completely filled with dye. The myocardium was diffusely injected. The right ventricle showed a deeper injection than the left ventricle.

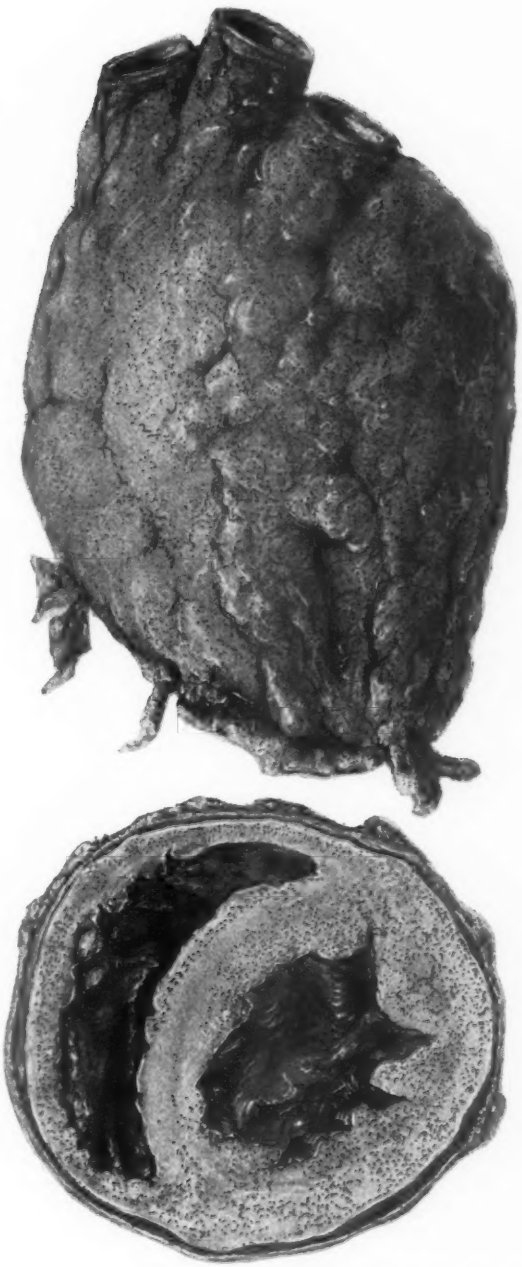

Fig. 11.—Protocol 11 (Dog No. 33-16). The collateral vascular bed was well injected. There is some injection of the myocardium, particularly the left ventricle.

The least injected portion of the heart was a zone adjacent to the endocardium of the left ventricle. Microscopical sections showed extensive injection of arteries and capillaries in the pericardial adhesions, in the entire thickness of the right ventricle and in the external two-thirds of the left ventricle. There was no fibrosis or infarction. The circumflex branch of the left coronary artery was completely occluded and the right coronary artery showed almost complete occlusion admitting only a very fine probe. The descending branches of the left coronary artery were intact.

Protocol 13.—Dog No. 33-144. Dec. 12, 1933: A wire loop and a silver clip were placed around the right coronary artery and the two major branches of the left coronary artery. A silver clip was placed around the septal branch, which in this dog was larger than usual. The lumen of each of these vessels was reduced about one-half. The burr was used on the epicardium and pericardium. The animal developed a pulmonary infection and died Jan. 11, 1934. Patchy areas of consolidation were present in the lung. The animal was injected. The pericardial cavity was obliterated. This obliteration was fibrous over the apex of the heart and the lateral surface of the left ventricle; elsewhere it was fibrinous. There seemed to be complete injection of the parietal pericardium and filling of the superficial branches of the coronary arteries, with extensive focal myocardial injection of both ventricles. The injection of the myocardium exceeded that seen in any of the normal hearts. Each of the major coronary arteries was partially constricted. The clip on the circumflex branch at its origin reduced the lumen at least one-half. The ramus descendens was markedly occluded, and it is questionable whether the obstruction had not been complete. The right coronary artery was markedly constricted. It was not patent to the smallest probe although the lumen contained dye. Microscopically the large and small superficial arteries contained dye. The capillary injection of both ventricles was focal, but in some sites it was extensive. It was significant that evidence of a collateral circulation appeared in three weeks from the original operation.

Protocol 14.—Dog No. 34-9. Jan. 25, 1934: Each branch of the left coronary artery was surrounded by a silver clip and a loop of wire. The lumen of each artery was reduced approximately one-half. The right coronary artery was partially occluded. July 11, 1934: The ramus descendens was completely occluded. Ventricular fibrillation occurred, and the heart stopped. Study of the specimen showed fibrous obliteration of the pericardial cavity except over the anterolateral upper portion of the left ventricle. A good injection of the parietal pericardium was obtained. Incomplete filling of even the superficial branches of the coronary arteries was found, and there was very little myocardial injection. The myocardial injection was no more than one finds in normal hearts. The right coronary artery was markedly reduced; the lumen was about 1 mm. in diameter. The ramus descendens of the left coronary artery was similarly reduced. Despite what was considered significant reduction in the lumina of the right coronary artery and the ramus descendens of the left, together with extensive pericardial adhesions, no significant anastomosis could be demonstrated through the adhesions. This failure in the development of collateral anastomosis was the only one obtained in these experiments. Microscopically the larger arteries contained dye. In superficial focal areas some capillary injection was found. The deeper portion of the myocardium was not injected. There was no evidence of fibrosis or infarction.

Protocol 15.—Dog No. 33-28. Apr. 15, 1933: A loop of periosteum was placed around the left coronary artery above its bifurcation. Hemorrhage from the aorta was encountered but was controlled. The endothelial surface of the parietal pericardium was scraped with a scalpel. The pericardium was sutured to the myo-

cardium. June 8, 1933: A mass suture was placed for the purpose of occluding the ramus circumflexus. Dec. 19, 1933: The right coronary artery could not be isolated. A mass suture was taken for the purpose of occluding it. Likewise a mass suture was placed for the purpose of occluding the ramus descendens of the left coronary artery. Feb. 6, 1934: Another attempt was made to occlude the ramus descendens of the left coronary artery by placing a mass suture. Oct. 1, 1934: The dog had been active but had lost weight. It was killed for study. The right coronary artery was normally patent. The ramus circumflexus of the left coronary artery was normally patent throughout its course. The ramus descendens was occluded by not more than one-third its cross-section. There was complete injection of the parietal pericardium and complete obliteration of the pericardial sac by dense fibrous adhesions. The superficial branches of the coronary arteries were filled with dye. There was very scanty incomplete injection of the myocardium, more marked in the right ventricle than elsewhere. Microscopically all arteries contained dye as did also many arterioles. Capillary injection of the epicardium was present. The capillary injection of the myocardium was scanty. The epicardium was greatly thickened and fused with parietal pericardium. The adhesions were richly vascularized. No myocardial fibrosis or infarction was found. This experiment would indicate that there was little or no need for the production of a collateral circulation.

DISCUSSION OF EXPERIMENTS

These protocols, recorded briefly as they are, indicate in a general way the results that were obtained in a considerably larger series of experiments and operations. The fatal nature of many of the experiments, the difficulty in the technical performance of the operations, the variety of the operative procedures that were evolved as the work progressed made it necessary to carry out a larger number of experiments than otherwise would have been necessary.

When we began these experiments, we desired to destroy or to obstruct the entire arterial coronary circulation and have a new collateral circulation develop to take its place. We did not succeed in doing this, but we almost succeeded. In one of the experiments about 85 per cent of the total cross-sectional area of both coronary arteries was occluded (right coronary artery completely occluded, ramus descendens completely occluded, ramus circumflexus markedly constricted), and this animal survived and was normally active. In several experiments complete occlusion of the ramus descendens was effected with recovery of the animal. Complete occlusion of the ramus circumflexus was effected with recovery of the animal. Complete occlusion of the right coronary artery was effected with recovery of the animal. In other experiments partial occlusion of both right and left coronary arteries was effected with recovery of the animal. This is the first time such extensive occlusions of the major coronary arteries have been effected experimentally. Disease can accomplish this in man provided the occlusions are gradual so that a compensatory circulation can develop.

In a series of experiments which is now in progress, total occlusion of the right coronary artery in one stage was tolerated, but in these experiments a collateral vascular bed had been prepared for the heart

at a previous operation. We believe this observation is of considerable significance because in our experience total occlusion of the right coronary artery in one stage has carried a high mortality in the dog. To this observation we should like to add another. We observed repeatedly that partial occlusion of the coronary arteries was better tolerated if the heart had been given a collateral bed at a previous operation. This statement was based on opinion obtained at the operating table, but it has been repeated so frequently that we are willing to present it as fact. On the basis of this evidence the presence of a collateral circulatory bed can be considered as a prophylaxis against the ravages of sudden occlusion of the major coronary arteries.

The experiments showed that vascularization of the myocardium from a collateral bed was slight and in some experiments almost completely absent if the coronary circulation was normal. *In other words, the blood vessels grow into the myocardium when the latter has need for more blood.* On the basis of one observation it would seem that such collaterals can be demonstrated by injection as early as three weeks after the collateral bed has been established.

Total occlusion of a coronary artery can be produced without fibrosis or infarction of the myocardium. In only a few experiments did an infarct supervene, and it may be assumed that the occlusion in these experiments was produced so abruptly that the collateral circulation was inadequate to keep the myocardium viable.

The anastomoses between the cardiac and extracardiac vascular beds were functional. If these vessels had not transmitted blood, infarcts would have been more common than they were. The heart must get a supply of blood from some source to preserve its contractility. For this reason also we believe the direction of flow in the collateral bed is toward the heart rather than away from it. However, it has been observed that under certain circumstances the direction of flow in the anastomosis can be away from the myocardium. Reference to this observation has been given in this paper. Additional evidence in reference to the direction of arterial blood flow in the collateral bed was supplied by the observation that a greater degree of injection in the myocardium was obtained in those regions of the heart from which the coronary artery supply was occluded. It is scarcely conceivable that the direction of the arterial current should be away from such areas of the myocardium poorly supplied with blood.

We found that the normal dog could sometimes, but not always, tolerate a reduction in size of about one-third of both coronary arteries carried out in one stage. With this reduction of the coronary circulation the myocardium remained viable and maintained its power of contractility. The high mortality in our experiments was obtained when a greater degree of constriction than this was used.

Multiple ligation of secondary branches of the right coronary artery, of the ramus descendens, or of the ramus circumflexus was not well tolerated. Peripheral ligations of the arteries was followed by the production of foci in the myocardium that became discolored. These areas undoubtedly lost their property of contractility, and fibrillation frequently followed. It should be pointed out that in the two groups of experiments in which the coronary blood flow was reduced, one by partial central occlusion and the other by peripheral ligation, a greater degree of reduction in the total coronary blood flow seemed to be possible if the occlusion was central than if it was peripheral. In other words, total coronary blood flow is one important factor, but distribution of coronary blood flow is another important factor in reference to survival. There must be an equal distribution of blood to different parts of the myocardium. In this respect peripheral occlusion of coronary arteries may act like a weak link in a chain. We were slow in appreciating this very important fact, and it required a high mortality to demonstrate it to us. We believe the collateral bed was effective in bringing about an even or balanced distribution of blood to various parts of the myocardium. This was accomplished in two ways: (1) by supplying the myocardium with blood from extracardiac sources and (2) by transporting blood from one region of the myocardium that had an adequate blood supply to another region that had a deficient blood supply. The tissues adherent to the heart can act like anastomotic bridges that connect one coronary artery with the other.

We made the observation also that the degree of constriction produced by a silver band around a coronary artery was to a certain extent progressive in degree. Edema and fibrosis at the site of the clip not infrequently led to complete or almost complete occlusion of a vessel within a few days or weeks. This undoubtedly accounted for some of the mortality in the experiments. We confirm the observation of Halsted[5] that the obstruction of a vessel surrounded by a metal band may become progressive and complete. Bands of periosteum placed around the coronary arteries produced scar tissue which did not seem to produce constriction of a progressive nature. Nor did the transplanted periosteum form any bone. The use of a specially molded clip made from sheet silver was found to be more satisfactory for our purpose than any other method. This clip usually could be found at reoperation, and the lumen of the clip could be reduced in successive stages. To help locate the clip at reoperation, a loop of silver wire was placed around the artery adjacent to the clip. Also, the wire could be pulled taut and twisted, and complete closure of an artery could be produced if the clip could not be isolated from the scar. The loop of wire sometimes changed its position so that total occlusion of the artery occurred. Several animals were

lost because of this. However, wire was preferable to silk because the latter lost its tensile strength when buried in the body for several months.

We believe that the epicardium and the endothelial lining of the parietal pericardium may act somewhat as a barrier to the growth of blood vessels into the myocardium. Blood vessels can penetrate the epicardium, but we believe, perhaps without adequate experimental proof, that a richer vascularization is found when pericardial fat is in intimate continuity with muscle fibers. Therefore, we removed the epicardium with special burrs. In some instances the epicardium was stripped from the myocardium in sheets. Extensive removal of the epicardium can produce extrasystoles, tachycardia, dilatation of the heart, and ventricular fibrillation. The heart should be given periods of rest to prevent the summation of these responses. Studies are now being carried out to determine whether or not cocaine or novocaine will block the impulses going into the heart when the epicardium is removed. For the removal of epicardium and endothelial lining of pericardium we found that special burrs were more satisfactory than other methods. It was not necessary to incise the myocardium, nor was it necessary to suture structures to the heart. The vascular bed that developed after removal of epicardium and lining of parietal pericardium did not constrict the heart if the removal of epicardium and endothelial lining of pericardium was done by mechanical methods. Dakin's solution[6] and other chemicals when introduced into the pericardial cavity produced a thick layer of scar tissue which interfered with the heart action. Such solutions should not be used. The question naturally arises as to how much this vascular bed adherent to the myocardium interfered with the motion of the heart. It might be stated that cardiac adhesions per se are usually of little or no significance so far as any demonstrable disturbance to the heart is concerned.* In these experiments the vascular bed could stretch sufficiently to avoid cardiac compression. Adhesions between the vascular bed and the chest wall when present in these experiments did not seem to be of significance, although the heart was not extensively bound to the thoracic wall.

We believe that we have sufficient experimental data to justify their application to human patients. These experiments open an entirely new field and a great many problems present themselves in a most urgent way for study. It would be hazardous perhaps to predict the significance of these experiments at the present stage of development, but we believe that they hold promise of overcoming in an effective way the dreadful mortality from disease of the coronary arteries. In general terms, what we are trying to do is to destroy the "Gleitorgan" effect of

*Cardiac adhesions are usually silent lesions and their importance has been overemphasized. Scar tissue adherent to the heart can disturb the heart in two ways: (1) By its constricting effect producing either acute or chronic cardiac compression. This may be brought about without any adhesions. Adhesions when present in this condition are silent and incidental. (2) By producing a harness of adhesions through which the heart pulls upon the thoracic wall.

the pericardium in order to give the heart additional power to build a collateral blood supply. We believe that many catastrophes inflicted by reduction of a coronary artery could be avoided if the myocardium had direct continuity with another vascular bed. A little blood properly distributed to the area where most needed might preserve the heartbeat, and then as time elapsed the blood supply would be augmented, and vigorous function might again be resumed. We believe our experiments have demonstrated that the collateral bed can become the major source of blood supply to the heart.*

SUMMARY

The heart was given a collateral vascular bed by operation. Almost total occlusion of both coronary arteries was effected with recovery when a collateral vascular bed was present. The significance of these experiments in the treatment of coronary occlusion is discussed.

The illustrations were made by Theodora Bergsland.

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*The first operation of this kind on a human being was performed by us at the Lakeside Hospital Feb. 13, 1935. This patient had coronary occlusion and angina pectoris. An attempt was made to give the heart a new source of blood supply.

THE PRODUCTION OF A COLLATERAL CIRCULATION TO THE HEART

II. Pathological Anatomical Study*

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IN THE preceding paper, it has been shown that extensive anastomoses between the coronary arteries and those of the parietal pericardium and mediastinum develop in surgically produced pericardial adhesions in dogs. It has also been shown that the patency of these anastomoses increases as the normal flow of blood directly from the aorta to the coronary arteries is reduced. These observations make it seem likely that the production of pericardial adhesions offers a means of providing the heart with an effective collateral circulation. If this be true, it would be well to examine the pathological anatomy of coronary disease in man to determine the practicability of the application of this procedure.

Ninety-four human hearts in which a major coronary artery had been occluded were studied. Early in the investigation it was discovered that neither the absence of infarction nor the patency of vessels excluded the possibility of remote major trunk occlusion. Hearts were examined in which old complete occlusion of the major coronary artery was not associated with corresponding infarction. In other hearts, large cicatrized infarcts indicated remote major trunk occlusion, but canalization of the thrombus and enlargement of collateral channels obscured the original site of obstruction. These ninety-four hearts were judged to have sustained major trunk occlusion either because the site of occlusion was identified, as was usually the case, or because the infarct was so large, so uniform in character, and so situated anatomically that despite our inability to determine the exact site of remote occlusion it could be regarded with certainty to have occurred.

The average age of the individuals upon whom this report is based is fifty-four years, and the range was from thirty-five to seventy-nine years. The age distribution does not differ significantly from that reported by other observers (Fig. 1). Men outnumbered women in the ratio of about 3 to 1, and whites outnumbered blacks slightly more than 4 to 1.

Not all of the ninety-four died primarily or solely of coronary occlusion. As shown in Table I, there were seven persons who died of diseases in no way related to coronary disease but who had nevertheless sustained major coronary occlusion. It is obviously not possible to say

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TABLE I

NO. OF CASES	RELATION OF CORONARY OCCLUSION TO DEATH
64	Coronary thrombosis was judged to be principal or sole cause of death.
18	Death from progressive heart failure contributed to coronary occlusion.
5	Death due principally to hypertensive heart disease.
7	Death from miscellaneous causes, not related to primary heart failure.

whether they would have died ultimately of progressive coronary disease or not. Five died of complications due to hypertension, and although post-mortem examination disclosed coronary occlusion, the coro-

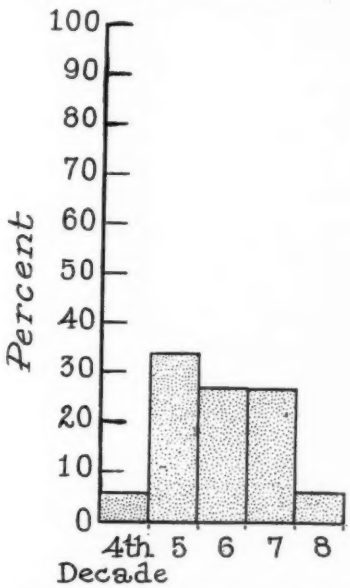

Fig. 1.—Percentile distribution of cases by decades.

nary disease was not judged to have been significant as a cause of death. In eighteen in whom death was due to gradually progressive heart failure associated with severe hypertension, coronary occlusion could not be regarded as the sole or principal cause of death. In sixty-four (68 per cent) of the entire group, coronary occlusion was judged to be the principal or sole cause of death.

Concomitant essential hypertension occurred with greater frequency than is indicated in Table I. There was clinical, pathological, or clinical and pathological evidence of hypertensive heart disease in 52 per cent of the entire group. This figure represents all of the individuals in whom there was anatomical evidence of essential hypertension, but, since detailed clinical records were not available in many instances, the actual incidence of hypertension may have been higher. An individual was

classified as belonging to the hypertensive group if there were repeated blood pressure observations with a systolic over 150 and a diastolic over 100 mm. of mercury, or if the heart weighed in excess of 500 gm. and arteriolar disease was present. Five hundred grams was arbitrarily selected as the maximum heart weight in the nonhypertensive group because it was found that in a number of instances in which hypertension was not observed on repeated clinical examination, during periods of

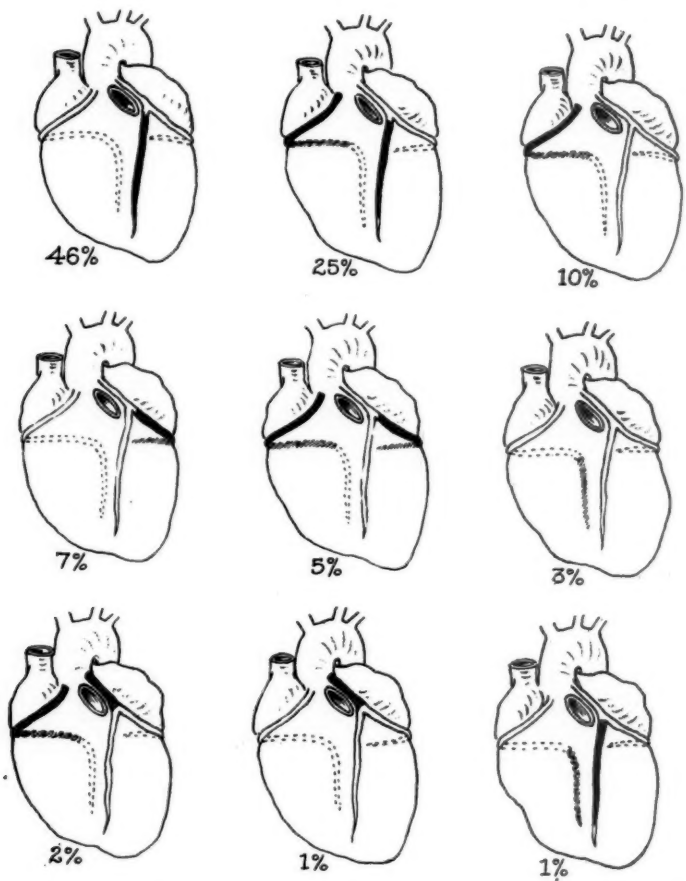

Fig. 2.—Percentile frequency of various sites of coronary arterial occlusion.

cardiac competence, and in which there was no disease of the smaller arteries, heart weights up to 500 grams occurred. It seemed likely therefore that the dilatation incident to myocardial ischemia predisposed in some instances to cardiac hypertrophy. It is of interest that the concomitant occurrence of essential hypertension and coronary occlusion was especially high in women (86 per cent) and in negroes (88 per cent).

The left coronary artery only was occluded in 54 per cent, the right only in 13 per cent, and both left and right in 33 per cent. Fig. 2

shows the sites of coronary occlusion. The divisions of the arteries most commonly occluded were the descending ramus of the left (72 per cent), the circumflex portion of the right (42 per cent), and the circumflex portion of the left (12 per cent).

It may be seen in Fig. 3 that the percentile incidence of left coronary occlusion decreased with age, with a corresponding increase in the relative percentages of right and of bilateral coronary occlusion. In those persons who lived beyond the age of sixty years there was less disparity between the numbers of right and left coronary occlusions and a relatively greater number of bilateral occlusions than present in the younger age periods. There was no significant difference between right

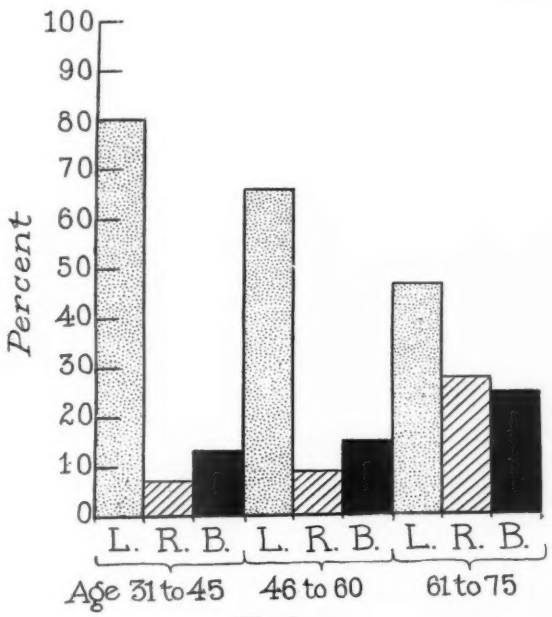

Fig. 3.

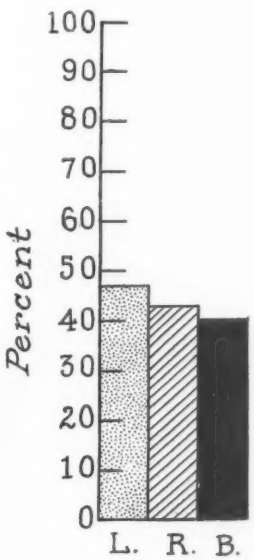

Fig. 4.

Fig. 3.—Percentile incidence of arteries occluded in each age group. (*L*, left coronary; *R*, right coronary; *B*, both.)

Fig. 4.—Percentile incidence of sudden death in cases of coronary thrombosis, in relation to artery occluded. (*L*, left coronary; *R*, right coronary; *B*, both.)

and left coronary arterial occlusion in relation to the occurrence of sudden death, and bilateral coronary occlusion was not associated with an increase in the occurrence of sudden death (Fig. 4).

The explanation of the increasing incidence of right coronary occlusion with age was not apparent. No figures were available for us to determine whether or not this is in accord with the findings of other observers. A study of the cases of bilateral coronary occlusion revealed that in all but five of the thirty-one cases the occlusions had not occurred simultaneously. The first occlusion, which had occurred with about equal frequency in the right and left coronary arteries, had developed

so slowly that the corresponding infarcts were not as extensive as would be expected considering the normal distribution of the vessel below the point of occlusion.

Despite the fact that the incidence of bilateral coronary occlusion increased with age, the incidence of sudden unexpected death from coronary occlusion decreased with age. Death was regarded as sudden when the period of cardiac invalidism was less than one week in duration. Fig. 5 reveals a sharp decline in the incidence of sudden death with increasing age. This is in accord with the observations of Conner and Holt.[1]

A plausible explanation of this apparent contradiction between the increased incidence of severe and extensive coronary sclerosis and the corresponding decreased incidence of sudden death from coronary occlusion is that the severity of the chronic myocardial ischemia probably determines cardiac incompetence before the terminal thrombosis occurs.

Of the ninety-four individuals in whom one or more coronary arteries were obstructed, only fourteen died following the first occlusion, and only eight of the fourteen died of uncomplicated coronary thrombosis. If these ninety-four individuals can be considered representative, it would appear that the majority (86 per cent) survive the first coronary occlusion. Moreover, in most of these (70 per cent of the entire group) there had been a period of cardiac competence varying greatly in duration after the primary occlusion. The significance of these observations in relation to the practicability of artificially inducing a collateral coronary circulation is obvious. The fact that 70 per cent of all persons having a major coronary occlusion not only survived the occlusion but had a subsequent period of myocardial competence would imply that most cases of occlusive coronary disease can be recognized as such. This is in accord with the studies of Wearn,[6] Levine and Brown,[4] and Conner and Holt. Furthermore, the disease is commonly recognizable before such extensive myocardial damage has been sustained as to determine chronic cardiac invalidism. In 117 cases Conner and Holt report a survival of only 21 per cent in a state of good health for more than five years after the first attack.

There is reason then to believe that relatively few (21 per cent) of the large number of individuals with occlusive coronary disease which can be recognized as such during good health escape cardiac invalidism longer than five years after their first attack. It cannot be said that all of those who die do so because of myocardial ischemia alone. In our series of cases 68 per cent of the entire group died of this cause.

Death in these individuals was commonly the result of additional coronary thrombosis with presumably such a concomitant increase in severity of coronary sclerosis that collateral circulation was no longer

adequate or because there was already such extensive myocardial obstruction that more was incompatible with circulatory competence.

There is abundant evidence that the coronaries are not end arteries but anastomose freely with one another (Gross[2] and Spalteholz[5]). In the event of the occlusion of a vessel which supplies so much of the heart, or such portions of the heart that complete ischemia would be incompatible with life, the physiological effects are determined by a combination of circumstances. The extent of the myocardial damage and, *pari passu*, the seriousness of the functional disturbance depend upon the suddenness of the occlusion, the patency of the collateral channels, and upon the blood pressure.

Fig. 5.—Percentile incidence of sudden death due to coronary occlusion, in relation to age.

Anatomically, two types of collateral channels develop in the dog as a result of surgically induced pericardial adhesions, and the same type of anastomoses might reasonably be expected to develop in man. The superficial anastomoses between the coronary arteries in the epicardium are increased, and the epicardial barrier between the coronary arteries and the arteries of the parietal pericardium and mediastinum is destroyed so that anastomoses between them occur. On anatomical grounds it would appear likely that such anastomoses would serve to protect the heart against the failure of collateral coronary circulation that usually determines death. Obviously such a collateral circulation could not be effective if there were significant coronary disease in the arteries

within the substance of the myocardium. Microscopical examination of many blocks from the myocardium in this group of cases indicated that significant sclerosis of the penetrating myocardial vessels was the exception rather than the rule. This is in accord with the opinion expressed by Karsner:[3] "The lesion appears to progress with diminishing severity from larger to smaller branches." The significant sclerosis and thrombosis were commonly confined to the superficial vessels, and the superficial vessels are the ones to which a collateral circulation by means of pericardial adhesions would be made available.

SUMMARY

On the assumption that thrombotic occlusion of a major coronary artery can be recognized clinically, it is probable that the diagnosis could have been made in life in eighty of these ninety-four patients. Only fourteen patients died as the direct result of the first major coronary occlusion. Of the eighty patients who survived the first occlusion, the question is whether or not they could have been protected against disastrous results from subsequent occlusions by the production of extracardiac coronary collateral circulation.

In thirty-seven of these eighty cases, concomitant disease or continued cardiac incompetence rendered the operative risk unjustifiable. The remaining forty-three patients might have been benefited by the production of the additional collateral circulation. With the exception of seven patients, who died of other causes, all died of subsequent attacks of coronary thrombosis.

This data, chiefly pathological, derived from this study of ninety-four cases of major coronary arterial occlusion would indicate that there was a period after the first coronary occlusion in the lives of forty-three individuals when the production of extracardiac coronary collateral circulation might have been feasible and beneficial.

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THE PRECORDIAL LEAD OF THE ELECTROCARDIOGRAM (LEAD IV) AS AN AID IN THE RECOGNITION OF ACTIVE CARDITIS IN RHEUMATIC FEVER*

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IN THE management of the patient with rheumatic fever, the most important clinical problem which presents itself is the recognition of active cardiac involvement. Bedside observation is sometimes adequate for decisive diagnosis. A count of the leucocytes and determination of the sedimentation rate of the red blood cells often furnish helpful information. Serial electrocardiography, with employment of the three standard leads, has proved to be a valuable method for following the effect of the rheumatic process on the heart.[1] We have found that the additional use of Lead IV has, in certain instances, revealed evidence of active carditis when, in the usual three derivations, either no changes in form were apparent in successive records or the alterations noted were regarded as equivocal.[2]

The use of chest leads in the study of the physiology of the heart is not a novel procedure. In his original work with the capillary electrometer, Waller[3] in 1887 placed the electrodes directly on the chest wall. The studies of Lewis, Drury, and Iliescu[4] on auricular fibrillation and flutter in man were materially furthered by the application of this method. It was Wolferth and Wood,[5] however, in 1932, who awakened interest in the use of chest leads for clinical purposes by demonstrating their value in the diagnosis of coronary occlusion. With the exception of our own preliminary note,[2] we have not seen any previous report on the use of Lead IV as an aid in the recognition of active myocardial involvement in rheumatic fever and in following its course.

In recording Lead IV, a stiff, rubber-covered spring was employed to retain in position two flat German silver discs, each 3 inches in diameter and fitted to receive the terminals of the lead wires. The skin at the sites of application was rubbed vigorously, first with alcohol, then with salt solution. The discs were covered with heavy flannel jackets saturated with warm saline. The resistance of the skin was usually under 2,000 ohms. Curves showing overshooting were discarded. The patient reclined on his back, either in the recumbent or semirecumbent position. The same posture was always assumed by any given patient when successive records were being made. The anterior (right arm) electrode was placed just to the left of the sternum, with its center approximately

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in the fourth interspace. The posterior (left arm) electrode was placed at a corresponding level in the back, to the left of the spine. Care was taken to place the anterior electrode always in the same position since a shift may vary the contour of the record obtained.[6] Slight shifts in the position of the posterior electrode are of little importance.*

Changes in the form of Lead IV which were considered to be abnormal were: an upright T-wave,† a negative T-wave deeper than 9 mm., a monophasic or notched QRS group, an R-T or S-T segment above the isoelectric line or one that was more than 2 mm. below this level.[7, 8] Any changes in form occurring in records taken on the same patient at different times were regarded as indicating alterations in the state of the myocardium. Such successive changes, however, while they show that the heart is affected and that the lesions are not in a quiescent state, are not specific for rheumatic fever.

Bed Patients.—Observations were made on thirty-eight patients with rheumatic fever in the wards of the hospital. None was taking digitalis or quinidine although a majority was receiving salicylate or pyramidon. Two hundred and ten electrocardiograms were made. By far the most frequently observed changes in Lead IV were alterations in the direction or voltage of the T-wave. In this series no example of elevation of the R-T or S-T segment occurred. The alterations in T_4 frequently appeared to indicate not only that changes were taking place in the heart muscle, but also the direction of the change as well. When the clinical condition of a patient suggested continued or renewed activity of the rheumatic process, this wave tended to assume an abnormal contour. When, on the other hand, other signs indicated healing of the rheumatic lesions in the heart, it generally approached or resumed the normal shape (Fig. 1).

In seven cases a change was noted in Lead IV only (Fig. 2). In sixteen cases changes were observed in the three standard leads as well as in Lead IV (Fig. 3); but in a number of these records significance could be attributed to minor variations in the first three leads, especially slight changes in the T-wave in Lead III, by finding gross alterations in Lead IV (Fig. 4).

In five cases changes were observed in the three standard leads, whereas the contour of Lead IV was not affected. Under these conditions the alterations in the first three leads consisted either of variations in auriculoventricular conduction time or of well-defined changes in the T-wave in Lead III. In ten cases no changes were seen in any lead.

*Since this work was completed, it has become our custom to use small, direct-contact metal electrodes and a saline jelly. The right arm electrode is placed on the precordium, as here described. The electrode on the left leg serves as the indifferent terminal. The complexes recorded in this way differ slightly in form from those obtained by the anteroposterior technic. But the criteria for normality and the character of the changes observed are the same.

†An upright T-wave in Lead IV has been observed in a number of normal children under twelve years of age. However, changes occurring in successive records retain their significance with respect to denoting alterations in the state of the heart muscle.

The series is small and no significance is attached to the relative number of cases in which each of these occurrences was noted. It is striking, however, that in twenty-three of thirty-eight cases the appearance of Lead IV was either the sole electrocardiographic index of active myocardial involvement or was important in confirming suggestive evidence supplied by the three standard derivations. It seems likely that had electrocardiograms been taken at more frequent intervals, the incidence of changes indicative of cardiac involvement would have been higher.

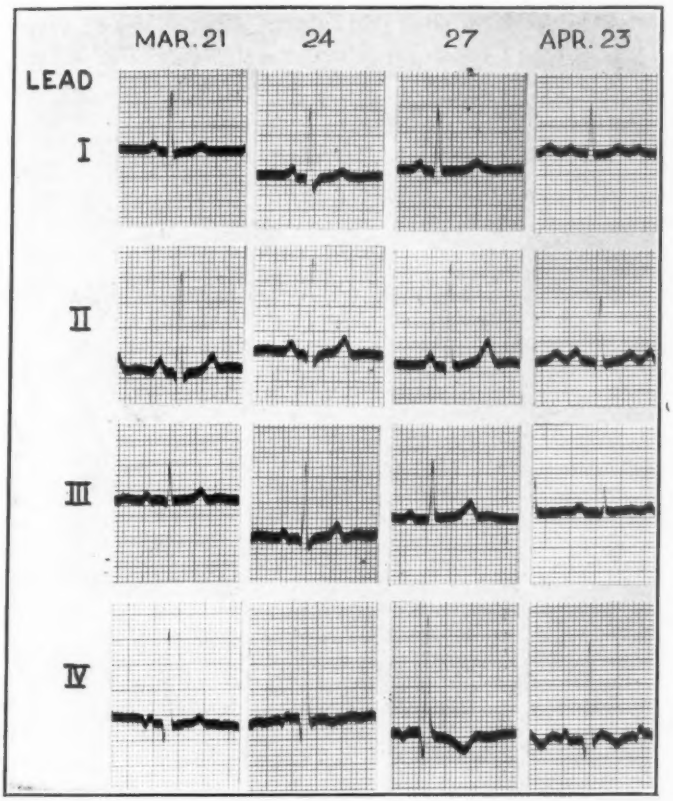

Fig. 1.—D. H., female, aged twenty-five years, was admitted March 20. She had attacks of rheumatic fever at eight and sixteen years of age with mild, recurring joint pains since. She bore two children without cardiac symptoms. Two months ago a heart murmur was heard. Two weeks before admission she had quinsy, followed soon after by severe joint pains and a rash.

On admission: Temperature, 98.8° F.; pulse, 100; blood pressure, 114/44. Heart enlarged; mitral systolic and diastolic murmurs. Typical erythema nodosum over arms and legs. *March 21:* Temperature, 101.4° F.; W.B.C., 16,200 with 76 per cent polymorphonuclears; Sedimentation rate, 87. Electrocardiogram: sinus rhythm; rate, 80; P-R, 0.16 second; T_4, upright. Aspirin, 3 gm. on this day. *March 24:* Temperature, 100° F. Joint pains less intense and erythema subsiding. Electrocardiogram: Rate, 85; P-R, 0.16 second; slight changes in the R-T segment in all leads; T_4, diphasic. *March 27:* Temperature, 100.2° F. Electrocardiogram: rate, 70; P-R, 0.16 second. Again slight changes in the R-T segment in all leads; T_4 at this time sharply inverted. *April 9-14:* Five teeth extracted, following which operation the temperature rose. *April 16:* W.B.C., 11,700, with 80 per cent polymorphonuclears. Sedimentation rate, 66. *April 23:* Aches and pains in the legs, shoulders, back, and fingers. Electrocardiogram: sinus tachycardia; rate, 105; P-R, 0.20 second. The rheumatic process evidently was reactivated following extraction of teeth. T-wave changes in all leads; P_4, upright; T_4, diphasic, with striking change in the contour of the R-T segment. *May 2:* Sent to convalescent home.

Ambulatory Patients.—A single record only was taken of thirty-four ambulatory patients with rheumatic heart disease who came to the Vanderbilt Clinic. In eight, deviations from the normal were observed in Lead IV only. In seven, changes were seen in the three standard leads, as well as in Lead IV. In eleven, changes were observed in the three standard leads and not in Lead IV. In eighteen, no changes were recorded in any lead. Single records of Lead IV on patients with rheumatic heart disease have been taken by others.[7, 9] Obviously, it is not possible, on the basis of only one electrocardiogram, to establish the presence of active carditis. Abnormalities, if present, merely indicate that the myocardium has been damaged.

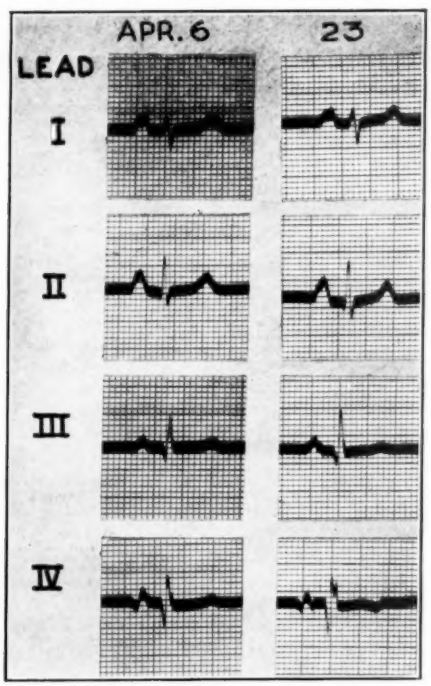

Fig. 2.—R. K., female, aged twenty-four years, was admitted April 4. She had rheumatic fever at the age of twelve years, with no known cardiac involvement. Polyarthritis recurred three months before admission and confined her to bed for a month. Since, she has noted dyspnea on exertion.

On admission: Temperature, 98.8° F.; heart rate, 80; blood pressure, 116/68. She was thin and pale. Heart enlarged. Signs of mitral and aortic valvular disease, with congestive failure. *April 6:* Temperature, 99.6° F.; W.B.C., 8,300, with 73 per cent polymorphonuclears. Sedimentation rate, 24. No drugs given. Electrocardiogram: sinus rhythm; rate, 65; P-R, 0.20 second; right ventricular preponderance; T_4 upright. *April 23:* Great improvement; patient very comfortable. Temperature, 99° F.; W.B.C., 6,500, with 65 per cent polymorphonuclears. Sedimentation rate, 23. No drugs. Electrocardiogram: rate 64; P-R, 0.20 second. First three leads similar in appearance to those observed April 6. Lead IV showed marked notching of QRS and inverted T-wave. *April 27:* Patient sent to convalescent home. *May 10:* Patient died in Peekskill Hospital. Report stated that she had heart-block.

Autopsy Cases.—Post-mortem examinations were made on seven additional patients observed in the hospital. In none had changes been noted in Lead IV only. In four, changes were seen in the first three leads, and

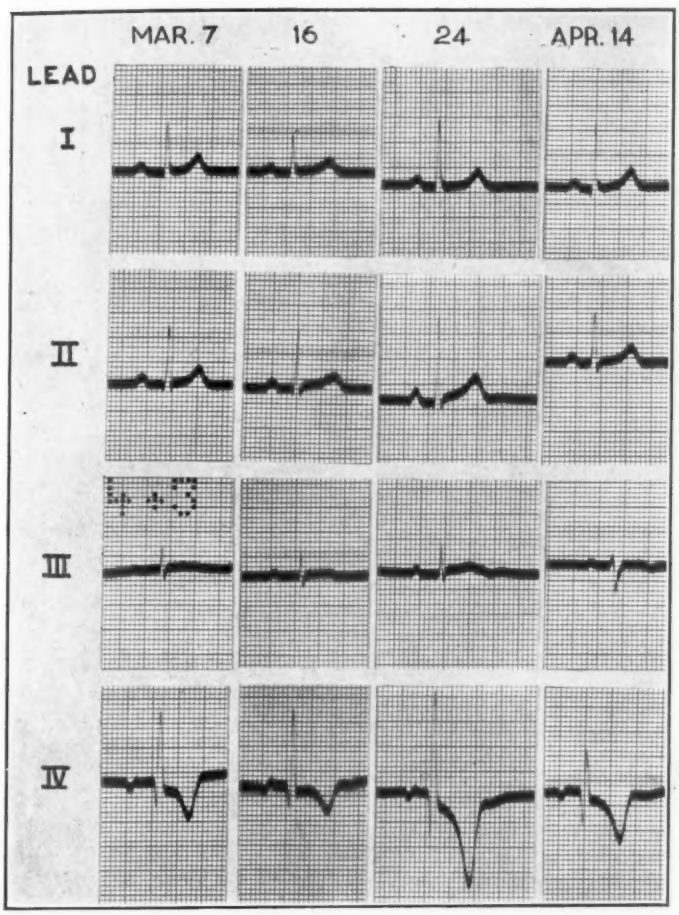

Fig. 3.—V. S. P., male, aged twenty-five years, was admitted March 6. He had two previous attacks of rheumatic fever, the first fourteen years, and the second nine years prior to admission, each lasting for several months. There were no cardiac symptoms. He complained of pain and swelling in various joints for one week.

On admission Temperature 103° F.; pulse, 84; blood pressure, 110/70. Tonsils large. Heart slightly enlarged. Systolic murmur at apex. All joints of arms and legs affected. W.B.C., 18,200. Throat culture yielded hemolytic streptococcus. *March 7:* Temperature, 103.2° F.; W.B.C., 17,900, with 85 per cent polymorphonuclears. Well-marked secondary anemia. Sedimentation rate, 45. Aspirin, 3.6 gm. on this day. Electrocardiogram: sinus rhythm; rate, 80; prolonged conduction, with P-R, 0.22 second. No changes in form. *March 16:* Temperature, 99.4° F. More comfortable. W.B.C., 18,000; sedimentation rate 48. Aspirin, 7.5 gm. on this day. Electrocardiogram: rate, 60; P-R, still 0.22 second; R-T segment, slightly elevated in Leads II and III; T_1 and T_2, slightly lower; T_4, less deeply inverted, with greater convexity of R-T segment. *March 24:* Temperature, 99.2° F.; W.B.C., 9,000, with 74 per cent polymorphonuclears. Sedimentation rate, 17. Aspirin, 9 gm. on this day. Electrocardiogram; rate, 55; P-R, 0.19 second; T-waves, higher in the first three leads, with elevation of the R-T segment in Leads II and III. In Lead IV, T-wave, deeply inverted, measuring 14 mm.; R-T segment, depressed. The voltage in Lead IV had become greater, but this is not due to overshooting, for the resistance was 900 ohms. *April 14:* Temperature, 99° F.; systolic murmur at apex persisted. Pyramidon, 3.6 gm. on this day. Electrocardiogram: rate, 55; P-R, 0.19 second; T_2, lower; S_3, deeper. R-T segment in Lead III, less sharply elevated. In Lead IV, T-Wave, less deeply inverted. R-T segment, no longer significantly depressed. *May 11:* Patient discharged from hospital.

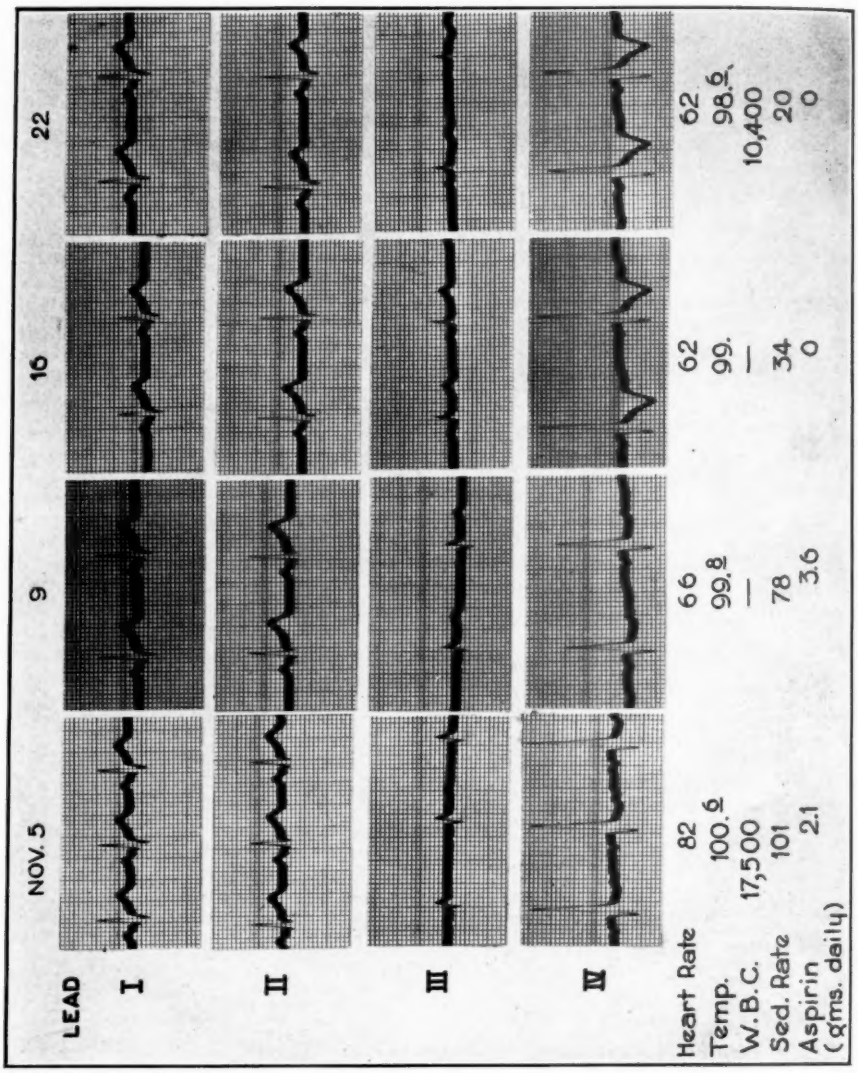

Fig. 4.—C. H., male, aged twenty-nine years, was admitted November 4. He had rheumatic fever at the age of twenty-two years and was in bed for three months, but there was no known cardiac involvement. An apical systolic murmur was first heard a year before admission. Nine days before admission he had a sore throat, followed six days later by mild joint pains and a temperature of 103° F.

On admission: Heart not enlarged. Systolic blow at apex. Blood pressure, 140/90. *November 5:* Electrocardiogram: P-R, 0.16 second; T_4, diphasic. *November 9:* Patient more comfortable. Electrocardiogram: P-R, 0.14 second. T_2 and T_3, a little higher. Very little change in Lead IV. *November 16:* Electrocardiogram: P-R, 0.15 second; slight changes in the form of R and T in Lead III; marked alteration in T_4 with return toward normal contour. *November 22:* Patient very comfortable. Electrocardiogram: P-R, 0.14 second. Again slight change in T_3. Lead IV as in previous record. *December 8:* Patient discharged from hospital. *December 19:* Patient remained well. Electrocardiogram: similar to the one of November 22.

the T-wave in Lead IV was upright. In three of these cases numerous Aschoff bodies were observed in the heart muscle; in the fourth, acute fibrinous pericarditis established the presence of active rheumatic fever although no Aschoff bodies were found. In the fifth case the three standard leads showed changes, whereas Lead IV was normal. In this patient, acute rheumatic pancarditis was present. In the two remaining patients, active rheumatic heart disease was suspected during life, but no changes were present in any of the four leads of the electrocardiogram. In neither instance were Aschoff bodies found at autopsy. One proved to be an example of verrucous endarteritis associated with quiescent valvular lesions; the other was a case of gonococcal endocarditis superimposed upon old, but inactive, rheumatic heart disease.

SUMMARY

1. In rheumatic fever, if successive electrocardiograms are taken, Lead IV may furnish evidence of active carditis when changes indicating active myocardial involvement are not observed in the standard three leads.

2. Frequently, gross variations in the contour of Lead IV indicate the significance of minor alterations in the three standard leads which might otherwise be regarded as of doubtful importance. This statement applies particularly to slight changes in the T-wave in Lead III.

3. On occasion, changes denoting rheumatic lesions in the heart muscle are present in the first three leads when no change is apparent in Lead IV.

4. In ambulatory patients with rheumatic heart disease, a single electrocardiogram may reveal evidence of myocardial damage in Lead IV only. On the basis of a single record, however, it is clearly not possible to establish the presence of rheumatic activity in the heart.

5. Changes in the electrocardiogram characteristic of myocardial involvement were found in five patients whose hearts at autopsy showed lesions of active rheumatism. In two patients, in whom active rheumatic carditis was suspected during life but was not found at autopsy, the electrocardiograms were normal.

6. In rheumatic fever the use of Lead IV is of clinical value as an aid in the recognition of active myocardial involvement and in following its course.

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THE FORM OF THE ELECTROCARDIOGRAM IN EXPERIMENTAL MYOCARDIAL INFARCTION*

II.† The Early Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery

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INTRODUCTION

WHEN one of the larger arteries of the human heart is suddenly occluded, the ventricular complex of the electrocardiogram undergoes a remarkable series of changes in form. Regarding the origin of these changes, which involve the QRS group as well as the RS-T segment and T deflection, there has been a great deal of speculation, and many different views as to the mechanism of their production have been expressed. A better knowledge of the factors that determine the form of the electrocardiogram in coronary occlusion will not only be of great service in the diagnosis of this condition, but will also help us to understand and to interpret the electrocardiographic abnormalities that occur in other types of heart disease.

The experiments upon which this series of articles is based were prompted by the discovery that infarction of the anterior wall of the human heart produces very striking and distinctive changes in the form of the initial ventricular deflections of precordial leads. Previous observations had shown that the ventricular complexes of such leads are similar in general outline to those obtained by leading directly from the anterior surface of the heart. We concluded that the use of direct and semidirect leads in experimental coronary occlusion could not fail to throw a great deal of light upon the questions at issue.

A full account of the principal methods employed in our experiments, which were carried out on large dogs, has been given elsewhere.[2, 4] Standard Lead I was taken simultaneously with all semidirect and direct leads and is represented by the upper curve in all records. The special leads were taken with a vacuum tube in the galvanometer circuit,[5] and the connections were so made that negativity of the exploring electrode produced an upward deflection. This electrode consisted of a small glass tube stoppered with salted kaolin, in which a short wick or a small piece

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†The first article of this series was published in the Am. Heart J., 9: 596, 1934. The observations reported here were briefly described in a preliminary report[1], and were also referred to in a paper read at a meeting of the Association of American Physicians[3]. Wood and Wolferth[3] have made a somewhat similar study.

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of sponge was embedded, and filled with a solution of sodium chloride. In this solution a silver wire coated with silver chloride was immersed. The indifferent electrode was of similar construction and was placed in contact with the subcutaneous tissues of the left hind leg. The sensitivity of the galvanometer was adjusted to give a deflection of 1 cm. for 20 millivolts when taking direct leads, and a deflection of 3 cm. for 20 millivolts when taking semidirect leads.

In describing our results, it is convenient to speak of the earlier and the later stages of myocardial infarction, the former term being used to designate those stages of the process that precede and the latter those that follow death of the fatally injured muscle. In this article we shall, for

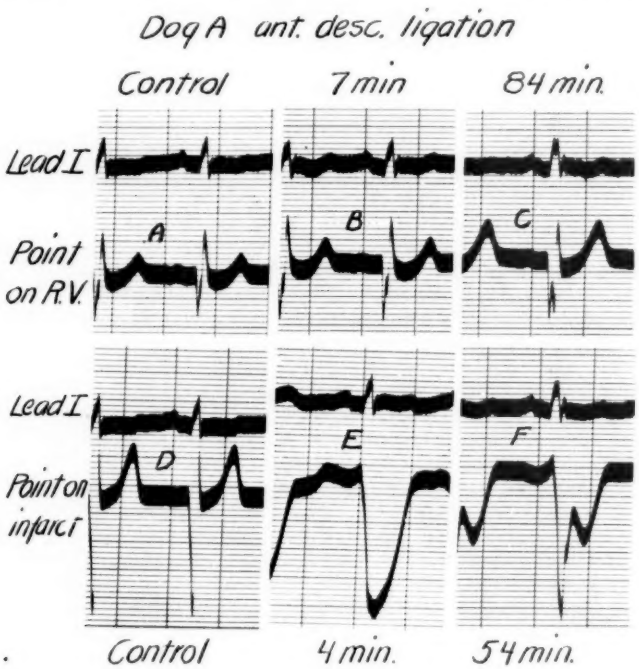

Fig. 1.—Experiment I (Dog A). The lower curve of each record represents a direct lead from the anterior surface of the exposed heart. In the upper row this curve is from a point near the base of the right ventricle, in the lower row from a point near the apex of the left ventricle. *A* and *D* are control curves; the time after ligation when the other curves were taken is indicated. In the direct leads a deflection of 1 cm. represents a potential difference of 20 mv. In this and all other figures the upper curve of each record represents standard Lead I.

the most part, confine our attention to the electrocardiographic changes that occur during the period immediately following coronary ligation.

DESCRIPTION OF EXPERIMENTS

Experiment I (Dog A).—Direct leads were taken from twelve different points widely distributed over the anterior surface of the exposed ventricles. The heart was then covered with a gauze pad (1 cm. in thickness) soaked in normal salt solution (0.9 per cent NaCl), and a series of four semidirect leads was obtained by placing the exploring electrode in contact with the pad. For the first of these

leads this electrode was placed upon the part of the pad which lay upon the base of the right ventricle; with each succeeding lead it was moved about 2 cm. nearer the apex. Neither the direct nor the pad curves showed anything unusual; the latter are reproduced in Fig. 2 (*A*, *B*, *C*, and *D*); and two of the former, one from a point on the base of the right and the other from a point near the apex of the left ventricle, in Fig. 1 (*A* and *D*).

After these preliminary observations the anterior descending branch of the left coronary artery was ligated at a point just distal to the origin of the artery which courses down the lateral margin of the left ventricle. The experiment was com-

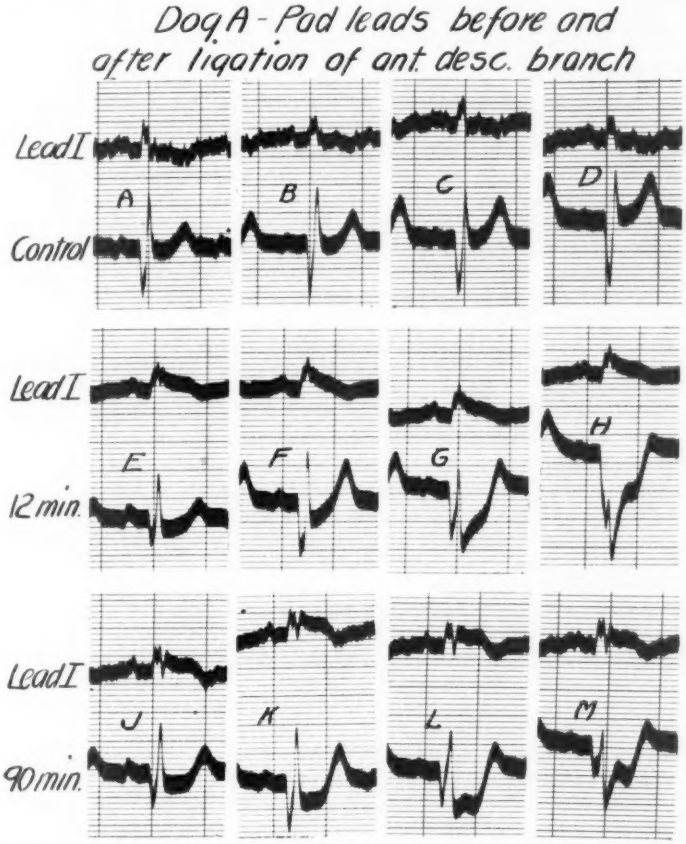

Fig. 2.—Experiment I (Dog A). Semidirect leads taken from a pad laid upon the exposed heart. In these leads a deflection of 3 cm. represents a potential difference of 20 mv.

pleted by taking direct leads from the points previously explored and additional sets of pad leads at intervals during a period of about one and one-half hours.

Within a few minutes the ventricular complexes of the direct leads from the region supplied by the ligated vessel and of the semidirect leads from that portion of the pad overlying this region were transformed into curves that are practically monophasic. This change is well illustrated by the curve shown in Fig. 1*E* which represents a direct lead from the central part of the affected region four minutes after the ligature was tied. This curve is characterized by the presence of a small initial summit, not present in the control curve (Fig. 1*D*) from the same point, and by

complete fusion of QRS and T into a single broad downward deflection. The sharp intrinsic upstroke of the control curve has completely disappeared. The curve from the same point taken fifty-four minutes after the ligation (Fig. 1*F*) is somewhat similar in outline, but downward displacement of the RS-T segment is much less pronounced, and there is a sharp upward movement which apparently represents the intrinsic deflection, reduced in amplitude and occurring between 0.02 and 0.03 second later than in the control curve.

The changes that took place in the curve from the apical portion of the pad were similar. In this case, however, no initial summit developed (Fig. 2*H* and *M*), and the displacement of the RS-T segment was somewhat less pronounced. The sharp upstroke of the control curve (Fig. 2*D*) is not clearly represented in the curves taken after ligation.

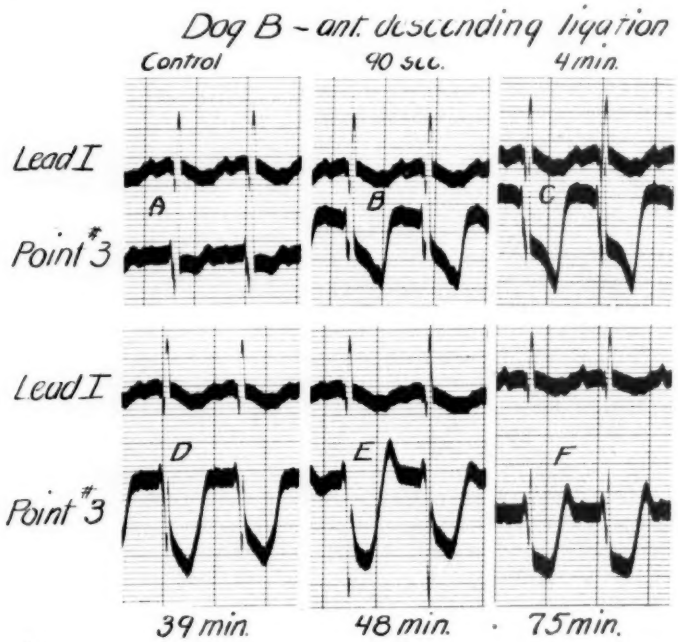

Fig. 3.—Experiment II (Dog B). Direct leads from a point on the left ventricle before and at intervals after the ligation of the terminal portion of the anterior descending branch of the left coronary artery.

Upon the form of the ventricular complexes of the direct lead from the base of the right ventricle, which receives its blood supply from the right coronary artery, and upon the complexes of the corresponding pad curve, the ligation had very little effect. In the case of the direct lead there was some increase in the size of the T deflection, and the initial deflections became conspicuously notched, but the significance of these minor changes under the circumstances obtaining is uncertain.

In the third pad lead the ligation was followed by definite downward displacement of the RS-T segment and by a reduction in the amplitude of the chief upstroke, which corresponds to the intrinsic deflection of direct leads. In the second pad lead there was slight downward displacement of the RS-T segment but no other striking change. In the direct leads from the marginal portions of the region supplied by the ligated vessel, the changes in the form of the ventricular complex were similar to those that took place in the third pad lead. It should be pointed

out, however, that in direct leads conspicuous downward displacement of the RS-T segment often occurs as a result of injury to the heart's surface produced by the application of the exploring electrode or by the continued pressure which it exerts. Such injury is particularly likely to occur when an electrode is applied to the surface of the exposed right ventricle whose anterior wall is continually in violent motion. From some portions of this chamber it is often exceedingly difficult to secure direct curves that are free of injury effects.

Experiment II (Dog B).—After exposing the heart in the usual way, a series of direct leads from the anterior surface was taken. The curves obtained were in no way unusual. One of these leads was from a point near the apex and midway between two small arteries which joined about one centimeter higher up to form the main trunk of the anterior descending branch of the left coronary artery. Several additional curves were taken from this point, and a loose ligature was then placed just above the junction of the arteries on either side of it. A curve from this same point was taken just before and another immediately after the ligature was pulled tight. Others were taken, first at shorter and later at longer intervals, over a period of about five hours. At the end of this time the animal died, apparently as a result of the prolonged anesthesia and artificial respiration. When the heart was removed, the infarcted region was plainly visible, particularly on the endocardial surface where it appeared as a pale area, some two or two and one-half centimeters in diameter, surrounding and involving the base of the anterior papillary muscle of the left ventricle.

All of the control curves from the point specified are similar, and all show a small initial summit (Fig. 3*A*). Ninety seconds after the ligature was tightened, there was already conspicuous downward displacement of the RS-T segment (Fig. 3*B*), but the deflections of the QRS group were not altered. During the next few minutes the RS-T displacement increased, and a definite reduction in the amplitude of the intrinsic deflection took place. In the later curves there was also some increase in the prominence of the initial upward movement. Forty-eight minutes after the ligation there was pronounced alternation in the form of the ventricular complex, and at this time a conspicuous summit at the end of the ventricular complex made its first appearance (Fig. 3*E*). Although the curves taken still later vary with respect to details, they are all similar in general outline to the curve shown in Fig. 2*F*, which was taken seventy-five minutes after the ligature was tied.

TABLE I

TIME OF ONSET AND AMPLITUDE OF THE INTRINSIC DEFLECTION IN EXPERIMENT II

TIME AFTER LIGATION	ONSET OF INTRINSIC DEFLECTION (SECONDS)	SIZE OF INTRINSIC DEFLECTION (MILLIVOLTS)
Control	0.003	54
90 sec.	0.001	60
110 sec.	0.002	54
3 min.	0.007	42
4 min.	0.009	40
39 min.	0.012	28
48 min.	0.013	34
75 min.	0.007	26
95 min.	0.007	34
2 hr.	0.009	36
2 hr. 23 min.	0.008	36
2 hr. 53 min.	0.010	36
3 hr. 43 min.	0.012	32
4 hr. 43 min.	0.019	30

In the curve taken at four minutes, the intrinsic deflection was for the first time distinctly later than in the control curves. In the subsequent curves the delay in the onset of this deflection increased until it reached approximately 0.01 second at forty-eight minutes. At seventy-five minutes, however, it was only about 0.005 second. From this time until the end of the experiment it varied between these two values. It is possible that some of these variations were due to the difficulty of placing the exploring electrode in contact with exactly the same spot at each observation. Table I gives the amplitude of the intrinsic deflection and the time of its onset with reference to the earliest ventricular deflection in standard Lead I for all the curves of the series.

Experiment III (Dog 36).—In this instance the main trunk of the anterior descending branch of the left coronary artery was ligated about one centimeter below the tip of the left auricular appendage. This operation was performed in the surgical laboratory under aseptic conditions. The small opening through which the ligation was done was immediately closed, and the chest wall was restored. No

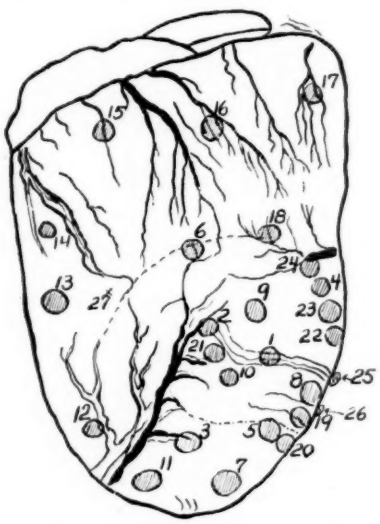

Fig. 4.—Experiment III (Dog 36). Outline drawing of the heart showing the location of the points explored by direct leads.

electrocardiograms were taken until four hours later. At this time the animal was brought to the electrocardiographic laboratory, where, after standard and precordial leads had been taken, the anterior surface of the exposed heart was explored by means of direct leads. From a number of points in the region supplied by the ligated vessel, curves were taken at intervals over a period of five and one-half hours, but all curves from the same point were found to be practically identical. The few minor exceptions appeared to be due to inaccuracy in placing the electrode on the spot it had previously occupied. We shall not need, therefore, to specify the time when each observation was made.

An outline drawing of the heart which shows the location of the points investigated is reproduced in Fig. 4, and samples of the different types of curves obtained in Fig. 5. The curves from points *3, 6, 7, 11, 12, 13, 14, 15, 16, 17,* and *18* were not obviously abnormal. It is convenient to divide the abnormal curves into two classes, but it should be noted that many of the curves obtained are transitional in form between those regarded as typical of the one class and those regarded as typical of the other.

The central portions of the infarct lay on the lateral margin of the left ventricle. In the curves from this region (points *8*, *19*, *20*, *22*, *25*, and *26*) the QRS group displays a conspicuous initial summit, and the intrinsic deflection or chief upstroke is of small amplitude. It is not possible to say with certainty whether or not the intrinsic deflection occurs slightly later than is usual in curves from the same region

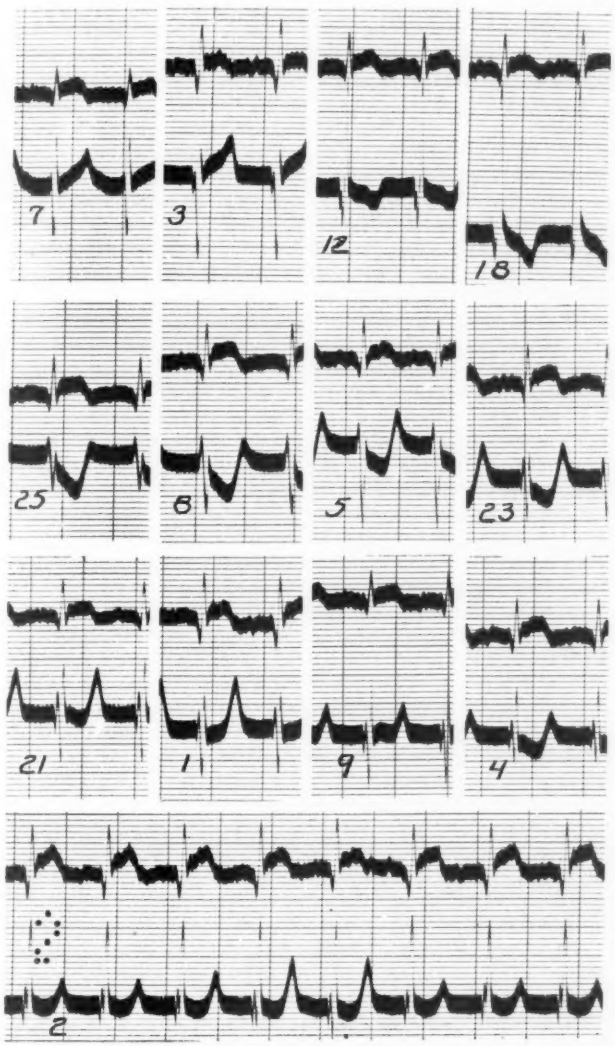

Fig. 5.—Experiment III (Dog 36). Curves obtained from various points indicated in Fig. 4.

in normal animals. The RS-T segment is displaced downward, and some of the curves show a distinct elevation at the end of the ventricular complex.

The curves from the peripheral portions of the infarct, of which that from point *21* (Fig. 5) is a characteristic example, are distinctly different in several respects. In these the QRS group shows two preliminary deflections, a sharp but small downward movement followed by a summit which corresponds in time to the initial summit

of the curves described in the preceding paragraph. In general the intrinsic deflection is larger in amplitude and is represented by a thinner line than in the curves just referred to. The RS-T segment is flat or shows a distinct downward slope and is followed by a sharp upright T of large size. Curves of this kind were obtained from points *1, 4, 9, 10, 21,* and *23* (Figs. 5 and 6). The curve from point *5* is similar but lacks the initial downward movement.

Near the margins of the infarct a slight shift in the position of the electrode often produced a pronounced change in the form of the ventricular complex. The first record from point *4* is of normal outline and resembles that obtained later from point *24;* the second is abnormal and similar to that from point *23.* Two of the three curves from point *2* show no definite abnormalities; in the other the QRS group is of almost exactly the same form, but T is different and shows striking rhythmic variations in size and shape (Fig. 5), which are undoubtedly due to the to-and-fro movements of the electrode caused by the rhythmic inflation of the lungs.

From points *10* and *19* curves were taken with the galvanometer connected in such a way that the direction of all the deflections was reversed (Fig. 6). Taken in this way, the curves from these points more closely resemble the ventricular complexes which, when they occur in the standard leads, have been considered characteristic of recent coronary occlusion. It will be observed that the ventricular complexes of standard Lead I and the reversed curve from point *19* are very similar in general outline.

In order to determine whether the muscle of the infarcted region was still living, direct leads were taken using a sharp copper wire, coated to within a short distance of the point with insulating enamel, as the exploring electrode. The form of the curves obtained when such an electrode is pressed against the surface of the heart in a region where the muscle is normal has been described elsewhere.[6] It will suffice to point out here that such curves show pronounced downward displacement of the RS-T segment and are often purely monophasic (Fig. 6). The intrinsic deflection may be greatly reduced in amplitude or may be absent. In a later article of this series we shall show that the curves obtained by leading directly from dead muscle are not altered when a sharp electrode is substituted for a soft one.

The curves obtained with a sharp electrode at points *8* and *10* (Fig. 6) show the same preliminary deflections as the corresponding curves obtained with an electrode of the ordinary type. Apart from these preliminary deflections they are purely monophasic. This indicates that the muscle at both points was capable of producing a large current of injury and that it responded to the excitatory process. When the sharp electrode was thrust through the ventricular wall at point *10,* the curve (Fig. 6) obtained was of the same type as those obtained from the left ventricular cavity of normal animals.[6] The curve from the right ventricular cavity (Fig. 6) in the neighborhood of point *27* shows an initial downstroke that is larger than usual, but no other notable peculiarities.

THE STANDARD AND PRECORDIAL LEADS

Since the changes in the ventricular complexes of the standard leads produced by coronary ligation in dogs have been extensively studied by others, we shall confine our remarks on this subject to a brief consideration of the changes observed in the three experiments described. Upon the form of the ventricular complexes of standard Lead I, taken with the heart fully exposed, the ligation had no significant effect either in the first experiment (Dog A) or in the second (Dog B). In the former, striking upward displacement of the RS-T segment in Lead I was present

after the ligation when this lead was taken while the heart was covered with a gauze pad soaked in saline. In the second experiment the effect of covering the heart with a pad was not determined. Leads II and III were not taken in either of these experiments. In the third experiment (Dog 36) the chest wall was completely restored immediately after the artery was ligated, and no electrocardiograms were taken until four hours later. At this time the heart rate was quite slow (about 50 per minute), probably because morphine had been given. The standard leads showed no striking abnormalities as long as the chest remained intact. When the heart was exposed, however, a large Q deflection and pronounced displacement of the RS-T segment appeared in Lead I. At the same time, the heart rate rose to approximately 200 per minute.

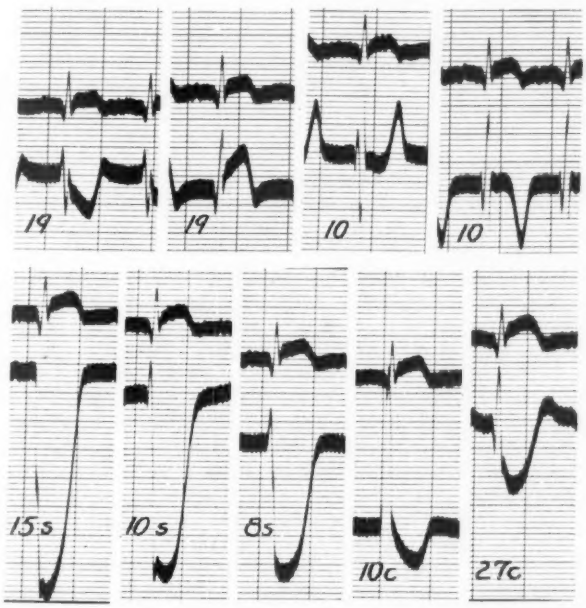

Fig. 6.—Experiment III (Dog 36). Curves obtained by leading from certain points indicated in Fig. 4. The curves of the upper row show the effect of reversing the galvanometer connections upon the form of the curves from points *19* and *10*. The curves of the lower row were taken with a sharp exploring electrode, which was pressed against the epicardial surface (*15s*, *10s*, and *8s*) or pushed through the wall into the ventricular cavity (*10c* and *27c*).

The appearance of RS-T displacement in Lead I after the heart was covered with a pad in the first experiment suggests that its absence when the heart was fully exposed was due to the lack of a satisfactory electrical contact between the anterior surface of the heart and the body tissues (see Wood and Wolferth[3]). In the third experiment, however, the RS-T displacement was absent when the chest was intact and present after the heart had been exposed, and it seems impossible that this difference can be explained by the large change in heart rate that took place when the chest was opened.

It is clear that any procedure which alters the distribution of the electrical currents produced by the heart muscle may or may not affect the form of the ventricular complex in a given lead depending upon the circumstances. Whether, in a given experiment, opening the chest and exposing the heart will diminish or accentuate the changes in the ventricular complexes of Lead I produced by ligation of the anterior descending branch of the left coronary artery would seem to depend chiefly upon the location of the infarct and of the contacts made by the heart with surrounding structures, but other factors are probably also important. After the heart was exposed in the third experiment, there was a striking resemblance between the ventricular complexes of Lead I and the inverse of the curves obtained by leading directly from the central portions of the infarct on the left margin of the heart. This resemblance was undoubtedly due to a similarity between the potential variations of the left foreleg and those at the surface of the infarct. When the chest was opened, the contact between much of those uninfarcted portions of the ventricular wall which faced toward the attachment of the left foreleg was broken, and the effect of the potential variations occurring at the epicardial surface in these regions upon the potential of this extremity was diminished or abolished. In the first experiment the infarcted region was presumably more directly anterior, and the effect of the potential variations occurring at its surface upon the potential of the left foreleg was therefore increased when the heart was covered with a pad.

In the third experiment precordial leads were taken immediately before the heart was exposed. The indifferent electrode was placed on the left leg, and the exploring electrode on the precordium, first in the midline, then over the apex beat, and finally still farther to the left. None of the resulting curves show distinct RS-T displacement. The first is certainly normal. In the last two, all the deflections are unusually small, and a distinct downward movement at the beginning of the QRS interval is absent. These curves were taken too soon after the ligation operation to preclude the possibility that some air still remained between the anterior surface of the heart and the chest wall.

Death Following Coronary Ligation.—No particular effort was expended on the study of the disturbances of rhythm that usually follow the ligation of a coronary artery, but a few observations made incidentally in the course of our experiments are worth recording. In the second experiment (Dog B) no disturbances in rhythm were observed at any time. In the first experiment (Dog A) ectopic beats of ventricular origin, represented in Lead I by complexes which vary greatly in form, were present in large numbers during the fifteen minutes immediately following the ligation. None were observed thereafter. In two other experiments (Dog C and Dog 48) in which the anterior descending

branch of the left coronary artery was ligated at a high level after the heart had been completely exposed, ventricular fibrillation occurred within less than two minutes. In one of these experiments the extrasystolic arrhythmia which preceded the onset of fibrillation was of very short duration; in the other instance it was either brief or absent. In this last experiment very pronounced alternation in the form of the ventricular complexes was observed in a direct lead from the affected area one minute after the ligature was tied (Fig. 7).

In the great majority of our experiments in which the anterior descending artery was ligated, the operation was done under aseptic conditions through a small opening in the chest wall. When the ligature was placed about the main trunk of the vessel at a high level, the immediate mor-

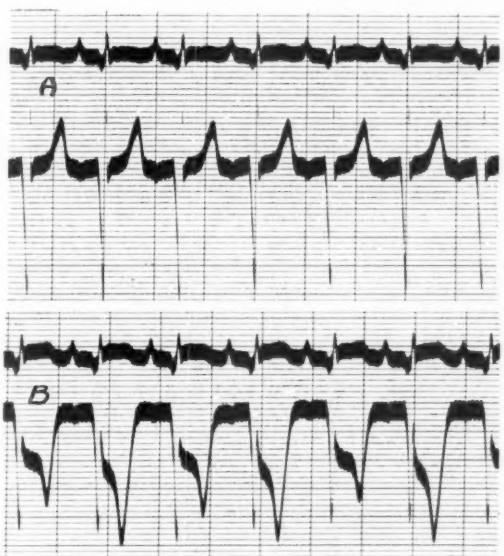

Fig. 7.—Dog C. Direct curves from a point on the left ventricle before (*A*) and 1 min. after (*B*) ligation of the anterior descending branch of the left coronary artery. In *B* the ventricular complex shows pronounced alternation. The heart was fully exposed when these curves were taken.

tality was very large. Seven of eighteen animals died before the chest could be restored, that is, within less than a half hour. In some instances the heart was still uncovered and under observation when it failed, and in most of these it was still contracting vigorously at the time when ventricular fibrillation developed. In others, however, the heart dilated and had practically ceased to contract before fibrillary movements began. Two animals died with symptoms of congestive cardiac failure, one thirty-six hours and the other four days after operation. One died fifteen hours after operation, probably of acute cardiac failure. Another died forty-eight hours after operation as the result of infection. Seven animals were killed after the anterior surface of the

heart had been explored by means of direct leads, and six of these were found to have large infarcts. In the other the infarct was small, probably because the ligature was not sufficiently tight to occlude the vessel completely.

In eight animals the ligature was placed around one of the larger branches of the anterior descending artery or about the main trunk of this vessel at a low level. Only one of these animals died during the operation. One died of infection four and one-half days after the ligation, and the remainder were killed after exposing the heart to obtain direct leads.

Our experience suggests that death from ventricular fibrillation is very much more likely to occur during the first half hour following ligation of a coronary artery than at a later time. It is during this period that extrasystolic disturbances appear to be most common. Ventricular fibrillation is much more often induced when the vessel ligated is a large one than when it is small. Death immediately after ligation is not always due to the onset of ventricular fibrillation; it is sometimes due to failure of the contractile mechanism without disturbances of rhythm.

DISCUSSION

The principles governing the interpretation of curves obtained by direct and semidirect leads of the kind employed in the experiments described have been adequately discussed in a previous article.[6] It was there shown that the deflections obtained by leading directly from the ventricular surface are profoundly altered when the superficial layers of the muscle beneath the exploring electrode are injured. The method used to produce the injury is immaterial. The major changes consist in a pronounced displacement of the RS-T segment and a conspicuous decrease in the amplitude of the intrinsic deflection. High grade injuries may cause this deflection to disappear. The form of the deflections which precede the onset of the intrinsic deflection is not altered. The magnitude of the changes in the RS-T segment and intrinsic deflection diminishes with the lapse of time, and they eventually disappear.

The changes induced by ligation of the artery that supplies the region with which the exploring electrode is in contact do not differ in any important respect from those that occur when this muscle is injured in some other way, and there is no reason to think that they have a different origin. Our observations indicate that certain minor differences exist but are not sufficiently extensive to prove that this is the case.

In the first experiment (Dog A) one of the changes produced by the ligation was the appearance in direct leads from the affected region of a small summit at the beginning of the QRS interval. In the second experiment (Dog B) a very thin small initial summit was present in the control curve; after the ligation this summit became distinctly larger. In the third experiment (Dog 36) a conspicuous initial summit was pres-

ent in all curves from the central part of the infarcted region. We believe that the appearance of a summit of this kind is due to a delay in the activation of the subendocardial muscle or to a decrease in the magnitude of the electrical forces which activation of this muscle produces.[6] In the first two experiments the intrinsic deflection in leads from the affected area occurred slightly later after the ligation than before, but we are not certain that the difference is significant. In two experiments (Dogs B and C) conspicuous alternation in the form of the ventricular complex of direct leads from the infarcted region occurred, and we have also called attention to the development, in such leads, of a prominent summit at the end of the ventricular complex. In the case of superficial injuries involving only the subepicardial muscle, we have not seen any of these changes, but it is unlikely that they occur only in association with the type of injury produced by destroying the blood supply to portions of the left ventricular wall.

It is hardly to be expected that the changes produced by injuring the superficial layers of muscle in a small, sharply circumscribed region will be exactly the same as those produced by ligation of an artery. The injury produced by cutting off the blood supply often involves the whole thickness of the ventricular wall and must vary greatly in degree from place to place, particularly at the margins of the affected area.

In the case of the left ventricle, infarcts old enough to have become clearly visible are as a rule more extensive on the endocardial than on the epicardial surface and frequently involve only the inner layers of muscle. It would, therefore, be most interesting to determine whether the changes in the ventricular complex produced by coronary ligation are the same in leads from the inner as in leads from the outer surface of the ventricular wall. Unfortunately, satisfactory leads from the endocardial surface are difficult to obtain. In a single experiment we determined the effect of ligating the main trunk of the anterior descending artery upon the form of the curve obtained from the cavity of the left ventricle by thrusting a sharp electrode through the wall. The curve taken before ligation was of the usual type[6] and displayed a deep U-shaped T deflection. After ligation this inverted T became somewhat smaller, but no other change occurred. The experiment was terminated prematurely by the onset of ventricular fibrillation.

Additional observations bearing upon the form of the curves obtained from the peripheral portions of left ventricular infarcts will be presented in a subsequent article. The curves from this region in the third experiment (Dog 36) differ from those obtained in other experiments in only one respect; they display a small downward movement at the beginning of the QRS interval. In all of the other curves of this class in our possession this downward movement is absent, and its significance is obscure. It is present in the curve obtained at point *10* by means of a sharp electrode (Fig. 6) and was obviously not produced by the sub-

epicardial muscle. No similar deflection occurs in the curve from the left ventricular cavity, which absence suggests that it did not depend upon the activities of muscle in distant parts of the heart but had its origin in those portions of the ventricular wall over which it was recorded. It was obtained over a large area, and a similar deflection is seen in some of the curves from points outside the infarcted region (Fig. 5). It was therefore probably present before and not produced by the ligation. Its direction indicates that the electrical forces responsible for it were produced while the excitation wave was spreading toward the exploring electrode rather than away from it. The only suggestion that we have to offer is that it may have been produced by activation of the anterior papillary muscle or of the trabeculae on the anterior endocardial surface of the left ventricular wall. Although the mechanism of its production is, therefore, not clear, its absence in other experiments indicates that it is not an essential characteristic of curves from the margins of a left ventricular infarct.

SUMMARY

The electrical activities of the heart muscle during the first few hours following ligation of the anterior descending branch of the left coronary artery were studied by means of direct and semidirect leads, taken simultaneously with standard Lead I.

During this period the principal changes in the form of the ventricular complex in direct and semidirect leads from the region whose blood supply has been destroyed consist in a pronounced displacement of the RS-T segment and a reduction in the amplitude of the intrinsic deflection or chief upstroke. Similar changes are observed in direct leads when the subepicardial muscle beneath the exploring electrode is injured in other ways.

A few hours after the ligation direct leads from the peripheral portions of the infarcted region show changes in the form of the QRS group and T deflection which are apparently characteristic and differ from those that occur in direct leads from the central portion.

Extrasystolic disturbances and ventricular fibrillation are much more likely to occur within the first half hour following ligation than later. Death during this period is not always due to the onset of ventricular fibrillation; it is sometimes due to asystole occurring without disturbances of rhythm.

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THE FORM OF THE ELECTROCARDIOGRAM IN EXPERIMENTAL MYOCARDIAL INFARCTION*

III.† The Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery

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THE chief purpose of this article is to describe and to discuss certain changes in the form of the ventricular deflections of direct and semidirect leads produced by ligation of the anterior descending branch of the left coronary artery. The changes that occur during the first few hours immediately following ligation of this vessel have already been described,[2] and we shall confine our attention here to those observed later when the parts of the ventricular wall that have been deprived of their blood supply no longer respond to the excitatory process.

The principal methods employed in our experiments have been described previously.[1, 2, 4] Standard Lead I was taken simultaneously with all direct and semidirect leads and is represented by the upper curve in all records. The direct and semidirect leads were taken with a vacuum tube in the galvanometer circuit,[5] and the connections were so made that negativity of the exploring electrode produced an upward deflection. The distant or indifferent electrode was placed in contact with the subcutaneous tissues of the left hind leg, and the sensitivity of the galvanometer was adjusted to give a deflection of 1 cm. for 20 millivolts when taking direct and of 3 cm. for 20 millivolts when taking semidirect leads.

In taking semidirect or pad leads the exploring electrode was placed firmly in contact with a gauze pad (about 1 cm. in thickness) soaked in physiological salt solution and laid upon the exposed heart. The pad was sufficiently large to cover the heart completely and to make contact with the surrounding structures. Four curves were usually taken. In taking the first of these, the exploring electrode was placed upon that part of the pad which lay over the base of the right ventricle; with each succeeding lead it was moved 1.5 to 2.0 cm. toward the apex along a line

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†For the first two articles of this series see Wilson, Johnston, and Hill[1] and Johnston, Hill, and Wilson[2]. The observations reported in this article were briefly described in a preliminary report[3] and were also referred to in a paper read at a recent meeting of the Association of American Physicians[4].

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parallel to the long axis of the heart. The final semidirect lead was therefore from that part of the pad which lay upon the apex of the left ventricle.

In several experiments a short study of the absolute refractory period was made in order to determine whether the infarcted muscle was capable of responding normally to stimulation. For this purpose we employed the method used by Wilson and Herrmann.[6] An inductorium arranged to give single shocks was connected to a rotating device which made it possible to obtain break shocks at a constant rate. These shocks were delivered to the heart through an electrode consisting of a pair of small fishhooks, bound closely together but insulated from each other, which

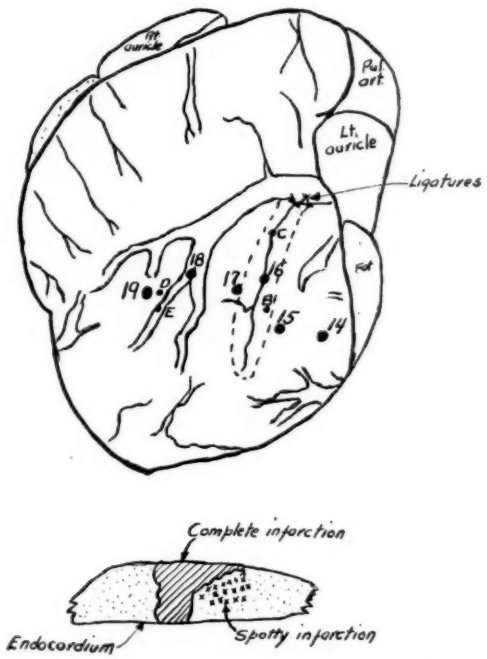

Fig. 1.—Experiment I (Dog 23). Outline drawing of the left anterolateral surface of the heart showing the location of the points from which direct leads were taken and the location of the points at which the refractory period was determined. The broken line marks the boundary of the infarcted region. Below is a sketch of a cross-section of the infarcted region about 1 cm. below the ligature.

were thrust into the superficial layers of muscle. When the rate of stimulation was adjusted so that it was only a little slower than the heart rate, each stimulus fell slightly later in the cardiac cycle than its predecessor. By measuring the time, with reference to the beginning of the QRS interval, of the latest ineffective and of the earliest effective stimulus, the approximate length of the refractory period was easily determined. The strength of the stimulus was varied by moving the secondary coil, which began to overlap the primary coil at a scale reading of approximately seven centimeters.

ILLUSTRATIVE EXPERIMENTS

Experiment I (Dog 23).—A small subdivision of the anterior descending branch of the left coronary artery was ligated. Four days later the heart was exposed, and its anterior surface was explored by means of direct leads. A series of semidirect leads was also taken. All of the semidirect and all but one of the direct curves were of the normal type. The single abnormal curve was obtained from the extreme left margin of the left ventricle. Since this region was not clearly visible, the animal was turned slightly so as to expose the left anterolateral surface of the heart. This procedure brought into view the ligated vessel and the pale zone of infarcted muscle surrounding it. Six additional direct leads were taken with the heart in this position. These curves are reproduced in Fig. 2. An outline drawing of the heart showing the location of the points from which they were obtained and the location of the infarct, and a diagrammatic sketch of a cross-section of the infarcted portion of the left ventricular wall, about 1 cm. below the ligature, are shown in Fig. 1.

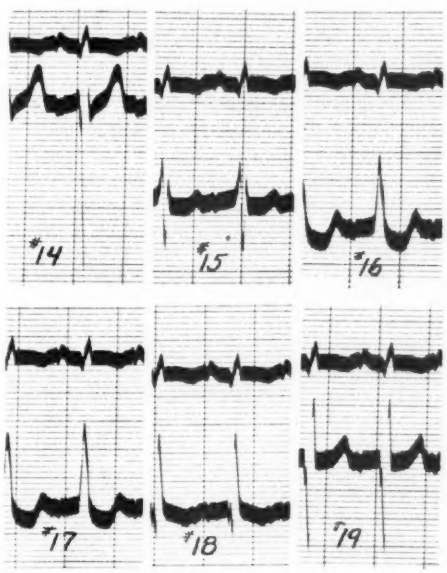

Fig. 2.—Experiment I (Dog 23). The upper curve of each record is standard Lead I. The lower curves represent direct leads from the points in Fig. 1 labelled with corresponding numbers. In all direct curves a potential difference of 20 mv. is represented by a deflection of 1 cm. The connections were always so made that negativity of the exploring electrode produced an upward deflection. In all records the time interval between successive vertical lines is one-fifth second.

The curves from points *14*, *18*, and *19* do not differ in any important respect from those usually obtained from the corresponding portions of the normal heart. The curves from points *16* and *17*, both of which lay within the boundaries of the infarcted region, are of an entirely different kind. In these curves the QRS group consists of a single tall summit, and there is no trace of a true intrinsic deflection. There is, in other words, no sudden upstroke, represented by a thin and barely visible line as in the curves from points *18* and *19*, which can be ascribed to the arrival of the excitatory process beneath the exploring electrode. The T-wave is represented by a U-shaped depression followed by a small elevation. These ventricular complexes closely resemble those obtained when the exploring electrode is thrust through the heart wall into the cavity of the left ventricle.[7]

In the curve from point *15*, which was near the margin of the infarct, the QRS group begins with an abnormally large upward movement and the intrinsic deflection is of unusually small amplitude. In our experiments curves of this type were most often obtained from regions where only the inner layers of the ventricular wall were infarcted.

The refractory period was tested at the four points labelled *B*, *C*, *D*, and *E* in Fig. 1. The last two points lay close together on healthy muscle. The first point, *B*, was very close to the margin of the infarct and the second, *C*, was well within its boundaries. The time of the latest ineffective and that of the earliest effective stimulus at each point are given in Table I. It will be seen that the healthy muscle yielded definitely lower figures than the infarcted muscle. The figures for point *C* vary with different tests, possibly because the position of the stimulating electrode varied slightly with different applications. Such minor discrepancies are common in experiments of this kind, and their cause is not easily determined.

TABLE I*

REFRACTORY PERIOD IN EXPERIMENT I (DOG 23)

POINT	CURVE NO.	COIL AT	HEART RATE	LATEST INEFFECTIVE STIMULUS	EARLIEST EFFECTIVE STIMULUS
D	990	6 cm.	192-193	0.148	0.153
E	993	6 cm.	186-188	0.155	0.157
B	988	6 cm.	195-198	0.177	0.181
C	989	6 cm.	195	0.204	0.209
C	991	6 cm.	188	0.198	0.202
C	992	6 cm.	187-188	0.177	0.180

*The secondary coil began to overlap the primary at a scale reading of approximately 7 cm. In this experiment the healthy muscle began to respond with the secondary coil at 12 cm. The infarcted muscle did not begin to respond until it was moved up to between 8 and 9 cm. The curve numbers are given to indicate the order in which the different tests were made. The measurements given in this and later tables were made for us by Dr. John Nyboer.

Experiment II (Dog 19).—In this instance the electrocardiographic study was made forty-eight hours after ligation of the main trunk of the anterior descending branch of the left coronary artery. The first curves taken showed long periods of idioventricular rhythm separated by very short periods of normal sinus rhythm. The idioventricular rate was approximately 190 per minute and only a little faster than the sinus rate. When the vagi were cut the sinus rate rose to approximately 240 per minute, and the abnormal rhythm was abolished. An idioventricular rhythm of this type was observed in many of our experiments. It was probably induced in part by the administration of morphine, which in the dog enhances vagal tone and promotes ventricular escape, and in part by effects produced by coronary ligation. In those experiments in which there was no myocardial infarction it was not observed.

The infarct was a very extensive one; it involved the greater part of the anterior surface of the left ventricle. On opening the chest it was noted that the affected region was paler in color and showed less contractile movement than the rest of the heart wall. A photograph of the inner surface of the left ventricle is reproduced in Fig. 3; it shows a large area of pale muscle largely covered by subendocardial hemorrhage. On the cut surface the pale muscle extended completely through the ventricular wall. The septum was not grossly involved, but close to its anterior attachment on the endocardial surface of the right ventricular wall a few islands of infarcted muscle were visible.

An outline drawing of the anterior surface of the heart showing the location of the infarct and of the points from which direct leads were taken is reproduced in Fig. 4, and samples of the curves obtained are shown in Fig. 5. The curves from points *6*, *7*, *11*, *12*, *13*, *14*, *17*, *18*, and *21* are not abnormal; in all of these the QRS group begins with a conspicuous downstroke and the intrinsic deflection is of large amplitude. The curves from points *1*, *2*, *3*, *4*, *5*, *8*, *9*, *10*, *15*, *16*, *19*, and *22*, which were on the infarcted portion of the heart wall, are similar in general outline to those obtained from the infarcted region in Experiment I. The first and only prominent deflection of the QRS group is upward, and T is definitely inverted in all but one instance. Many of these curves, however, differ from the corresponding curves of Experiment I in one respect. The QRS group displays a small but sharp upstroke, which apparently represents the intrinsic deflection greatly reduced in

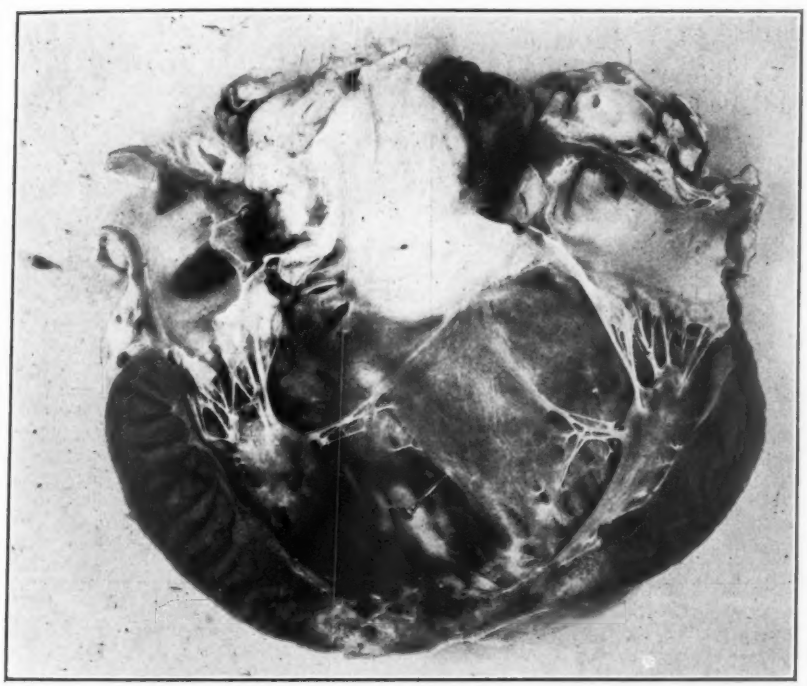

Fig. 3.—(Dog 19.) Photograph of the endocardial surface of the left ventricle. A pin at the right margin of the infarct marks the attachment of the septum to the anterior ventricular wall.

amplitude. In some instances this upstroke gives rise to a conspicuous notch on the descending limb of the initial summit (Fig. 5, Curves *2* and *8*); in others it occurs at the end of this deflection and begins below the baseline (Fig. 5, Curves *1* and *5*). The curve from point *20*, unlike the other curves from the infarcted region, shows a very small initial downward movement.

A set of four semidirect or pad leads was also taken. In the first of the curves so obtained the QRS group begins with a large downward movement; in the second the initial downward movement is small; in the last two it is absent and the ventricular complexes resemble those obtained by direct leads from the surface of the infarct. In standard Lead I the most prominent deflection of the QRS group is a large initial downward movement, or Q-wave. Before the vagi were cut the T

deflection was sharply inverted (Fig. 5, Curves *1 and 14*), but afterward the inversion was less pronounced. In Lead III the first and most prominent deflection of the QRS group was upward, and T was a pointed summit.*

The location of the points at which the refractory period was tested is shown in Fig. 4, and the measurements of the corresponding curves are given in Table II. These points have been divided into three groups. At the points of the first group (points *K, L, D, B,* and *H*) the duration of the refractory period was about 0.14 ± 0.02 second. At the points of the second group (points *E, F, Q, O,* and *N*) it was somewhat greater. At three of the four points (*A, G, M,* and *P*) of the third group no responses could be elicited; at the fourth point, *A*, the length of the refractory period varied with different tests, possibly because the stimulating electrode was not accurately replaced.

TABLE II

REFRACTORY PERIOD IN EXPERIMENT II (DOG 19)

POINT	CURVE NO.	COIL AT	HEART RATE	LATEST INEFFECTIVE STIMULUS	EARLIEST EFFECTIVE STIMULUS
K	947-3	6.75 cm.	240-244	0.121	0.130
L	948-1	6.75 cm.	231-238	0.117	0.133
L	949-1	6.75 cm.	232-236	0.131	0.151
D	945-1	6.75 cm.	238	0.123	0.134
D	951-1	6.75 cm.	231	0.134	0.141
D	952-2	6.75 cm.	229-231	0.132	0.145
B	943-2	8.25 cm.	244-245	0.126	0.169
H	947-2	6.75 cm.	238-240	0.128	0.164
E	946-1	6.75 cm.	240	0.144	0.182
Q	952-1	6.75 cm.	228-232	0.174	0.175
F	946-2	6.75 cm.	240	0.166	0.177
O	950-2	6.75 cm.	226-234	0.178	0.190
N	950-1	6.75 cm.	234-240	0.185	0.188
A	943-1	8.25 cm.	242-244	0.173	0.197
A	944-1	6.75 cm.	242	0.209	No responses
A	945-2	6.75 cm.	242-244	0.185	0.208
G	947-1	6.75 cm.	239-240	0.243	No responses
M	949-2	6.75 cm.	230	0.243	No responses
P	951-2	6.75 cm.	230	0.255	No responses

Experiment III (Dog 29).—The electrocardiographic studies were made four days after ligation of the anterior descending branch of the left coronary artery. Before the chest was opened for the purpose of taking direct leads, the standard limb leads and a set of three precordial leads were taken. In taking the precordial leads, the indifferent electrode was placed on the left hind leg; the exploring electrode consisted of a copper disk about one inch in diameter which was sewn under the skin of the precordium. For the first precordial lead this electrode was placed in the midline at the midprecordial level; for the second, directly over the apex beat; and for the third, about seven centimeters to the left of the apex beat. In all three precordial curves the prominent downstroke with which the QRS group of the precordial electrocardiograms of normal animals ordinarily begins was absent; the ventricular complexes were similar to those obtained later by leading directly from the surface of the infarcted region. The ventricular complexes of the standard leads were similar to the curves of the Q_1 T_1 type frequently obtained in cases of

*Standard Leads I and III of this animal (Dog 19) were reproduced in the first article of this series.[1] See Fig. 7*E* of that article. The standard curves of Dog 29 (Experiment III) are shown in Fig. 7*J* of the same article. In all the articles of this series the same numbers are employed in referring to the animals used in our experiments.

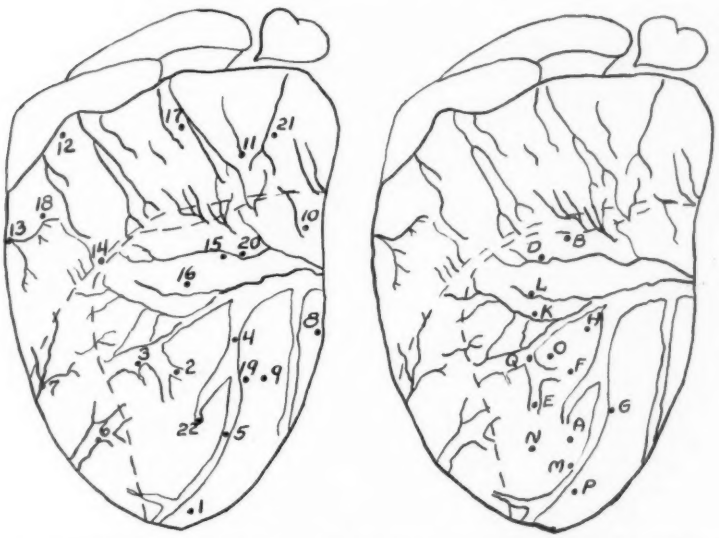

Fig. 4.—Experiment II (Dog 19). Outline drawings of the anterior surface of the heart showing the location of the points from which direct leads were taken (on the left), and of the points at which the refractory period was determined (on the right).

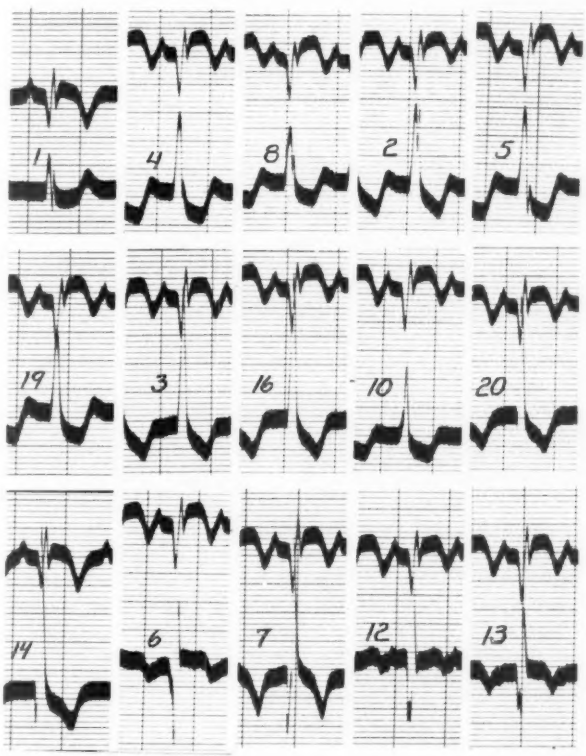

Fig. 5.—Experiment II (Dog 19). Direct leads from the points in Fig. 4, which bear the corresponding numbers. The upper curve of each record is standard Lead I. The curves numbered *1* and *1½* were taken before, the remainder after cutting the vagi.

infarction of the anterior wall of the human heart;[8] there was a very large Q deflection in Lead I and a small R and deep S in Lead III.

When the heart was exposed, it was observed that a large part of the anterior wall was abnormally pale, relatively immobile, and usually firm in consistence. It was subsequently found that the lower third of the posterior wall showed similar changes. When the heart was opened, the involvement on the inner surface of the left ventricle was seen to correspond in distribution to the involvement of the outer surface. On the endocardial surface of the free wall of the right ventricle a few small areas of infarction were found near the attachment of the septum; the septum itself did not appear to be involved.

The approximate boundaries of the infarcted region and the location of the points explored are shown in Fig. 6. The curves from points *7*, *8*, *9*, *10*, *11*, and *17*, which were outside the affected region, were of the normal type; in these the QRS group showed a characteristic intrinsic deflection preceded by a conspicuous downward movement (Fig. 7). The curves from points *1*, *2*, *3*, *4*, *5*, *6*, *12*, *13*, *14*, *15*, *16*, *18*, and *19*, all within the boundaries of the infarct, were of the same type as those ob-

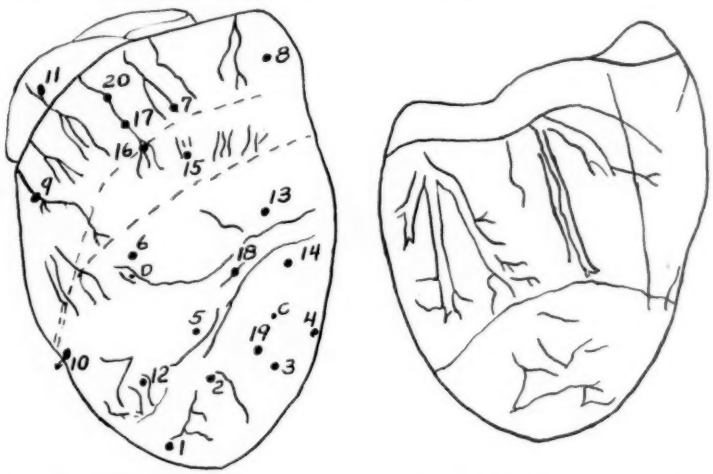

Fig. 6.—Experiment III (Dog 29). Outline drawings of the anterior (on the left) and posterior (on the right) surfaces of the heart showing the location of the points from which direct leads were taken and the location of the points at which the refractory period was determined. The upper broken line in the drawing on the left marks the upper boundary of the infarct; the lower broken line marks (approximately) the anterior attachment of the ventricular septum. In the drawing on the right the upper boundary of the infarct is marked by a solid line.

tained from the infarcted region in the experiments already described. They displayed no true intrinsic deflection and no conspicuous downward movement during the QRS interval; the sole deflection of the QRS group was upward.*

Instead of testing the refractory period at a large number of points as in Experiment II, only three points were stimulated, but the strength of the stimulus was varied through a wide range. One of the points investigated (point *C* near point *19*) was near the apex and in the central part of the infarcted region. The second point (point *D* near point *6*) was close to its margin, and the third (point *7*) was just outside its boundary. The figures which define the refractory period at these three points for stimuli of various strengths are given in Table III. In the case of point *7* a great increase in the strength of the stimulus had no appreciable effect upon the duration of the refractory period. At point *D* the refractory period was

*Some of the complexes of the curve from point *16* showed a small initial downward movement; in other complexes this deflection was absent.

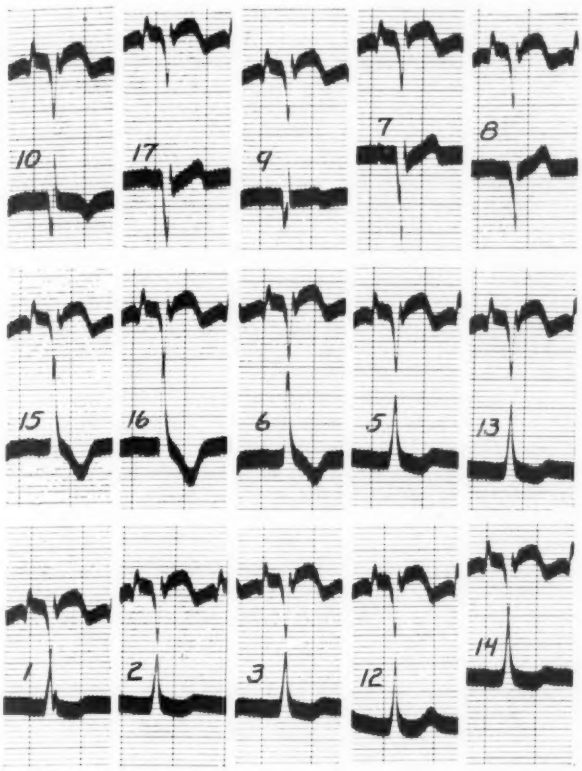

Fig. 7.—Experiment III (Dog 29). Direct leads from the points in Fig. 6, which bear corresponding numbers. The upper curve of each record is standard Lead I.

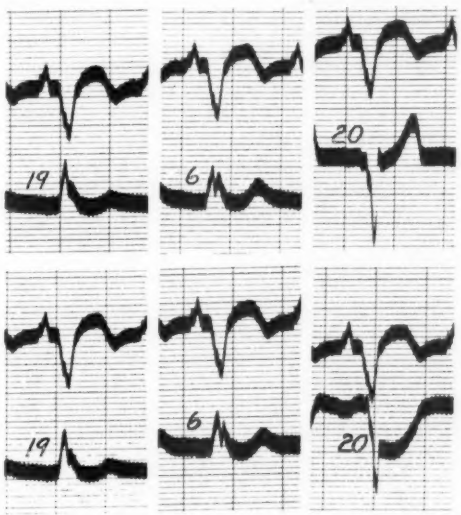

Fig. 8.—The lower curves represent direct leads taken before (upper row) and after (lower row) burning the muscle beneath the exploring electrode. The upper curve of each record represents standard Lead I. These curves were taken after the right branch of the His bundle had been cut. The direct curves were obtained by leading from the points in Fig. 6, which bear corresponding numbers.

definitely longer than at point *7* for stimuli of all strengths. The figures obtained are not entirely consistent, but apparently there was a tendency for the refractory period to shorten as the strength of the stimulus was increased. At point *C* only the strongest stimuli produced responses, and the period during which the muscle was refractory even to these was very long.

TABLE III

REFRACTORY PERIOD IN EXPERIMENT III (DOG 29)

POINT	CURVE NO.	COIL AT	HEART RATE	LATEST INEFFECTIVE STIMULUS	EARLIEST EFFECTIVE STIMULUS
7	R11	8 cm.	167	0.146	0.169
7	R14	8 cm.	158-160	0.183	0.185
7	R20	6 cm.	154	0.148	0.177
7	R19	4 cm.	153-155	0.159	0.170
7	R27	1 cm.	147	0.161	0.172
7	R28	1 cm.	148	0.058	0.176
D	R13	8 cm.	161-162	0.218	0.223
D	R17	8 cm.	158	0.249	0.258
D	R24	6 cm.	152-153	0.201	0.219
D	R18	5 cm.	158-159	0.201	0.210
D	R23	4 cm.	152-153	0.199	0.200
D	R25	1 cm.	146-148	0.195	0.212
C	R15	8 cm.	160	0.364	No responses
C	R21	6 cm.	155	0.295	No responses
C	R16	5 cm.	158	0.336	No responses
C	R22	4 cm.	152	0.289	0.332
C	R26	1 cm.	146	0.287	0.300

After the right branch of the His bundle had been cut in order to determine the effect of the infarct upon the form of the levocardiogram,[1] it was decided to adopt a different method of studying the condition of the muscle at or near the three points where the refractory period had been measured. Direct leads were taken from points *19*, *6*, and *20* immediately before and again immediately after the superficial layers of muscle surrounding each of them had been burned with a hot iron. At point *20* the injury resulted in pronounced downward displacement of the S-T segment and a conspicuous reduction in the amplitude of the intrinsic deflection (Fig. 8); at points *6* and *19* it produced no change whatsoever in the form of the ventricular complex (Fig. 8). It may be concluded that the muscle at point *20* was living, but that the superficial muscle at points *6* and *19* was dead, or at least incapable of responding to the natural excitatory process. It is therefore probable that stimulation at these last two points produced responses only when the strength of the stimulus was increased to a point where a current of stimulating value flowed in the nearest muscle that was still living.

COMMENTS

We have recently discussed[7] in some detail the principles that govern the interpretation of the galvanometric curves obtained by epicardial and semidirect leads of the kind employed in the experiments described in this article. It has been pointed out that the conspicuous downstroke which immediately precedes the intrinsic deflection in direct leads from the epicardial surface of the normal ventricular wall represents the spread of the excitatory process from within outward through that portion of the wall subjacent to the exploring electrode. The polarity

of these electric forces is such as to make the epicardial surface positive with respect to the endocardial surface and to points distant from the heart. The intrinsic deflection itself represents the sudden change in the potential of the exploring electrode which occurs when the arrival of the excitatory process at the epicardial surface brings these forces, and hence the electromotive force across the ventricular wall, to an end, and thus allows the exploring electrode to assume the potential of the adjacent portions of the ventricular cavity. When the ventricular wall beneath the exploring electrode is dead, it does not respond to the excitatory process, and the endocardial and epicardial surfaces undergo similar variations in potential. The curves obtained from the epicardial surface then resemble those obtained from the adjacent portions of the ventricular cavity; there is no conspicuous downward movement during the QRS interval, and no true intrinsic deflection occurs.

According to this view, the large initial summit of the QRS group in direct leads from infarcted portions of the ventricular wall represents potential variations practically identical with those that take place in the ventricular cavity and is due to the suppression of the electrical forces normally produced by the outward spread of the excitation process through that part of the ventricular wall with which the exploring electrode is in contact. When this deflection is the sole deflection of the QRS group and is unnotched, it is assumed that all the muscle lying between the exploring electrode and the ventricular cavity is dead, or at least that it no longer responds to the natural stimulus. When this deflection displays a conspicuous notch ending in a sharp upstroke, as in some of the curves obtained in Experiment II (Dog 19), it is assumed that some of this muscle is still responding, but whether a small amount of muscle is producing electrical forces of normal magnitude or a large amount of muscle is producing electrical forces of subnormal magnitude is not easily determined. It is clear that even normal muscle will not respond unless there is some route by way of which the excitatory process can reach it; in cases of the kind under consideration we cannot, therefore, suppose that we are dealing with islands of healthy tissue completely surrounded by dead tissue. We may, however, be dealing with the converse, islands of dead tissue separated by layers of living muscle. It should be noted that the duration of the QRS group in leads from the infarcted region is not obviously increased, and, if any muscle in this region responded, the delay experienced by the excitation wave in reaching it must have been relatively slight. In all of our experiments there was an exact correspondence between the region which yielded abnormal curves of the kind described and the region which showed gross signs of infarction. There is no reason to suspect that the abnormalities noted were in any way dependent upon involvement of the branches of the His bundle, of their major subdivisions, or even of the Purkinje plexus.

They were apparently due directly to the infarction of the ordinary muscle of the ventricular wall and the resulting disappearance of the electrical forces normally produced by the muscle affected.

In most of our experiments the RS-T segment and the T deflection of the curves from the infarcted region were represented by a U-shaped depression, sometimes followed by a small summit. In some instances, however, there was no definite displacement of the RS-T segment, and T was frankly upright. Curves from the left ventricular cavity usually display final deflections of the former kind.

It was our hope that studies of the refractory period of the infarcted region would yield important information regarding the ability of the affected muscle to respond to the excitatory process. It soon became apparent, however, that such studies had very little if any value. It is obvious that, if the strength of the stimulus is sufficiently increased, the current flowing will rise above threshold value even in those parts of the heart most distant from the stimulating electrode. If several points on the surface of the infarcted region are found to differ as regards the apparent duration of the refractory period, or with respect to the strength of the stimulus required to produce a response, the differences found may depend either upon differences in the condition of the muscle at these points, or merely upon variations in the distance of the point stimulated from healthy muscle. It is probable that the reduction in the length of the refractory period observed in our experiments when the stimulating electrode was moved from the central toward the peripheral portions of the infarcted region has no significance. This is certainly true in the case of Experiment III, in which the form of the ventricular complexes obtained by leading directly from the two points in the infarcted region at or near which the refractory period was determined was not altered by burning the muscle upon which the exploring electrode rested.

In the experiments in which ligation of the anterior descending branch of the left coronary artery produced a very large infarct, the QRS group of standard Lead I began with a large downstroke, or Q deflection. It is perhaps worth noting that the apex of this deflection and that of the initial summit of the curves obtained by leading from the central portions of the infarct were always nearly simultaneous. This relation suggests that the large Q deflection and the initial summit of the direct leads have a similar origin.

SUMMARY

One to four days after ligation of the anterior descending branch of the left coronary artery or one of its subdivisions, the anterior surface of the dog's heart was explored by means of direct and semidirect leads. In taking these leads, the exploring electrode was paired with an in-

different electrode placed on the left hind leg, and the connections were so made that relative negativity of the former electrode produced an upward deflection in the completed record.

The curves obtained under these circumstances by leading directly from the epicardial surface of the infarcted region have a characteristic outline. The initial and usually the sole deflection of the QRS group is a tall summit. The downward movement which normally precedes the intrinsic deflection in direct leads from the ventricular surface is absent. The intrinsic deflection is likewise absent, or is greatly reduced in amplitude in which case it is often represented by a deep notch on the descending limb of the initial upward deflection. The RS-T segment and T-wave are usually represented by a U-shaped depression, sometimes followed by a small summit.

Curves of similar form are obtained when the exploring electrode is separated from the epicardial surface by a pad of gauze soaked in physiological salt solution or by the precordial tissues of the intact chest wall.

The curves in question are very much like those obtained by introducing the exploring electrode into the cavity of the left ventricle. They owe their characteristic form to the absence of the electrical forces normally produced by the portion of the ventricular wall deprived of its blood supply.

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THE CEREBRAL BLOOD FLOW IN MAN AS INFLUENCED BY ADRENALIN, CAFFEIN, AMYL NITRITE AND HISTAMINE*

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ALTHOUGH there is a considerable literature dealing with the action of various drugs on the blood supply to the brain, most of it is based upon experiments conducted on animals under an anesthetic. Observations on man have been indirect and, for the most part, fragmentary. Changes in spinal fluid pressure, or in the tension of oxygen in the internal jugular vein, have given presumptive evidence of alterations in blood flow, and studies on the changes in caliber of the cerebral blood vessels at operation have yielded interesting data. Much more questionable are deductions derived from observations of the action of drugs on systemic blood pressure or on the circulation in the skin and other organs of the body, for previous studies from this laboratory have shown that the cerebral circulatory response to either nervous or chemical stimuli may be the opposite of the response of blood vessels elsewhere in the body.[1]

The effect on the cerebral circulation of numerous important drugs has not been investigated, and among those that have, a confusion of testimony exists. Results of animal experimentation are often not applicable to clinical problems. The securing of accurate information from human subjects is of extreme importance, because of its bearing on the treatment of those conditions in which the blood supply to the brain is endangered. The chief clinical interest lies in knowing the effect of a drug on the volume of blood flowing through the brain, for a defective supply of blood and of oxygen quickly interferes with cerebral activity.

MATERIAL AND METHODS

The device which we have used for registering changes in blood flow is a thermoelectric flow recorder previously described by one of us.[2] It consists essentially of a fine wire stilet with an electrically heated tip. This stilet is thrust through a hollow needle into the lumen of the internal jugular vein. A constant electric current is applied to the tip of the stilet, sufficient to heat it to a temperature a degree or two

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above that of the blood. As the blood flows past the heated tip of the stilet, the tip is cooled. The faster the blood flows, the cooler the tip becomes; the slower the blood flows, the hotter the tip becomes. The temperature of the tip is measured by means of thermojunctions in series with a galvanometer. In order that a change in body temperature should not be misinterpreted as a change in flow, the cold junction is mounted on the stilet behind the hot junction; it then becomes possible to measure not the absolute temperature of the tip, but the difference in temperature between the heated tip and the body of the stilet. This difference in temperature varies only slightly with changes in body temperature but greatly with changes in blood flow.

The instrument records changes in the velocity of the surrounding stream. If, however, the cross-section area of the stream remains constant, changes in velocity may be interpreted as changes in volume flow. The tip of the stilet in our experiments was in the internal jugular vein close to its point of exit from the skull, a situation where only slight changes in the caliber of the vessel could occur, for where the vessel pierces the skull, it has essentially rigid walls. We believe, therefore, that we are warranted in interpreting changes in velocity as being due to changes in volume flow.

The data obtained are only roughly quantitative. They furnish no absolute values for volume flow; they indicate only the direction and general magnitude of alterations in volume flow. Because it is impossible to duplicate exactly the position of the stilet in the vein, records from separate experiments are only roughly comparable, as regards the magnitude of the changes. They are, however, strictly comparable as regards the direction of these changes. Respiratory movements and blood pressure were recorded simultaneously with cerebral blood flow.

This study was conducted on patients in the Neurological Unit of the Boston City Hospital, most of whom were subject to epileptic seizures. In each case, the subject gave his full consent to the procedure carried out.

EPINEPHRINE

Well known is the fact that adrenalin acts in general as a vasoconstrictor and produces pallor of the skin. Concerning affairs inside the cranium, the testimony in the literature has been somewhat confusing; only the most recent animal experimental work need be quoted. The primary action of adrenalin on pial arterioles, as on those elsewhere, is one of constriction. This is shown by local application to the pia mater (Forbes, Finley and Nason[3]) and by the experiments of Finesinger and Putnam[4] in which with the pressure of the perfused

blood maintained at a constant level, injected epinephrine caused a 44 per cent decrease in the volume of blood flowing through the head, and a 10 per cent decrease in the diameter of pial arteries. When, however, the increase of blood pressure was unrestricted, intracarotid injection of epinephrine caused a 13 per cent dilatation of pial vessels, and simultaneously an 85 per cent constriction of the vessels of the animal's ear.[3] These experiments indicate that a rise in blood pressure can overcome epinephrine vasoconstriction within the head but not outside. They suggest that the drug increases the cerebral circulation. With an instrument of the same general type as that used here, Schmidt and Pierson[5] have found that epinephrine injected intravenously produces an increased blood flow through the medulla of cats.

In eleven instances we injected a solution of epinephrine chloride intravenously. The results were unequivocal. In every case, there was an abrupt and great acceleration of blood flow. In eight instances, the amount injected, from 0.1 to 0.2 c.c. of a 1/1,000 solution, was sufficient to cause a sharp increase in blood pressure and in pulse rate. The curves representing blood flow and blood pressure were so similar in form that it seems evident that the increase in flow was in the main secondary to the increase in systemic blood pressure.

One of the records obtained is produced in Fig. 1. Following the injection of 0.1 c.c. of a 1/1,000 solution of epinephrine, there was a marked and sudden increase in blood flow. The fact that the blood flow curve is flatter at the top than the curve of blood pressure is possibly due to the characteristics of the flow recorder, for it has a "ceiling" beyond which pronounced increases in flow do not register correspondingly great changes in temperature.

The amount of epinephrine which we injected in our first experiments was undoubtedly greater than the amount secreted into the blood stream by the adrenals, and, therefore, the experiments do not represent physiological conditions. On three occasions we used much smaller doses, from 0.01 to 0.005 of a 1/1,000 solution. In each instance there was a moderate increase in flow without, however, a corresponding and simultaneous increase in blood pressure. The latter either fell or remained constant. The heart rate increased. Our evidence, therefore, indicates that in man the intravenous injection of adrenalin in amounts too small to raise blood pressure, as well as in larger nonphysiological dosage, produces an increase in cerebral blood flow.

CAFFEIN

Because clinicians have found that caffein is valuable for patients having the Cheyne-Stokes type of respiration, it has been assumed that

caffein acted to improve the cerebral and especially the medullary circulation. The experimental work with caffein has, however, been confusing.

Finesinger[6] has reviewed the literature. His own study showed that the response of the pial vessels in cats differed with the type and extent of the anesthesia and with the initial blood pressure. When the animal had recovered from ether, caffein injected intravenously caused the pial artery to constrict momentarily and then to dilate. In human subjects, Stevenson and his coworkers,[7] using a tambour covering a skull defect, obtained a drop in intracranial pressure, and Loman and Myerson,[8] a fall in spinal fluid pressure with no change in internal jugular venous

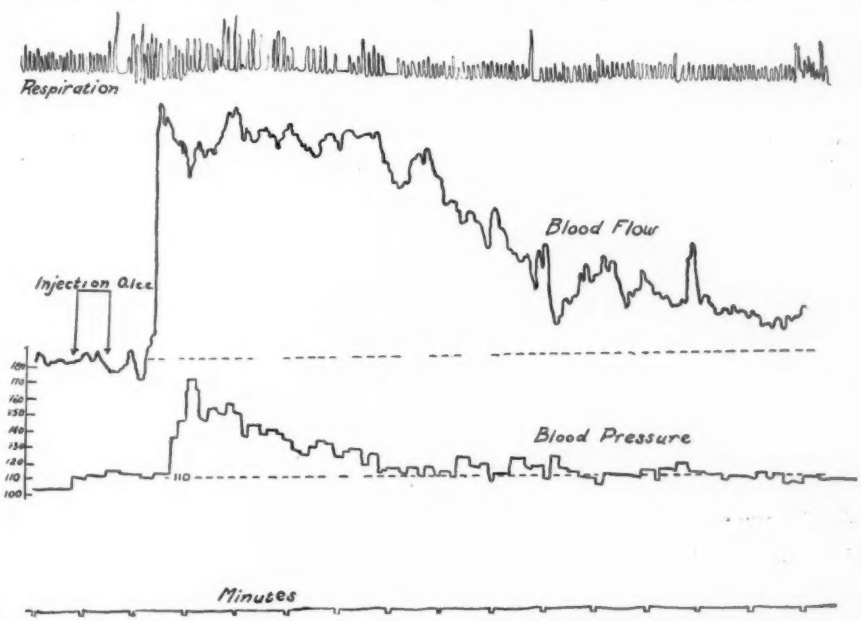

Fig. 1.—Effect of large dose of adrenalin on cerebral blood flow.

The tracing labeled "blood flow" is a record of the blood flow through an internal jugular vein. Above this is a record of chest movements. Below is a record of systolic blood pressures taken by the auscultatory method with the cuff on the upper arm. The maximum increase from the level at the time of injection was 60 mm. The bottom record gives time in minutes. The arrows indicate the period of injection.

pressure. These authors conclude that caffein causes a decrease in brain volume. However, such a fall in intracranial pressure could be caused by vasoconstriction due to a lowered blood CO_2 resulting from a caffein-induced hyperpnea.[1] Finesinger and Putnam,[4] using monkeys and keeping blood pressure constant, found that caffein caused an increase in cerebral flow of 116 per cent. There is no experimental evidence in the human subject to show whether the net result of the action of caffein on blood vessels, on respiration, and on blood pressure produces an increase or a decrease in cerebral blood flow.

Six experiments were conducted in which 0.5 gm. caffein sodium benzoate was injected intravenously. In five of the tests, within a minute, there was a gradual fall in flow. In all but two instances, after from two to ten minutes of diminished flow, it again increased to or slightly above its preinjection level (Fig. 2). Of particular importance in these observations is the fact that in all the cases the caffein caused a slight elevation of blood pressure.

A decrease in cerebral blood flow in the face of an increased blood pressure must mean that a cerebral vasoconstriction occurred due, per-

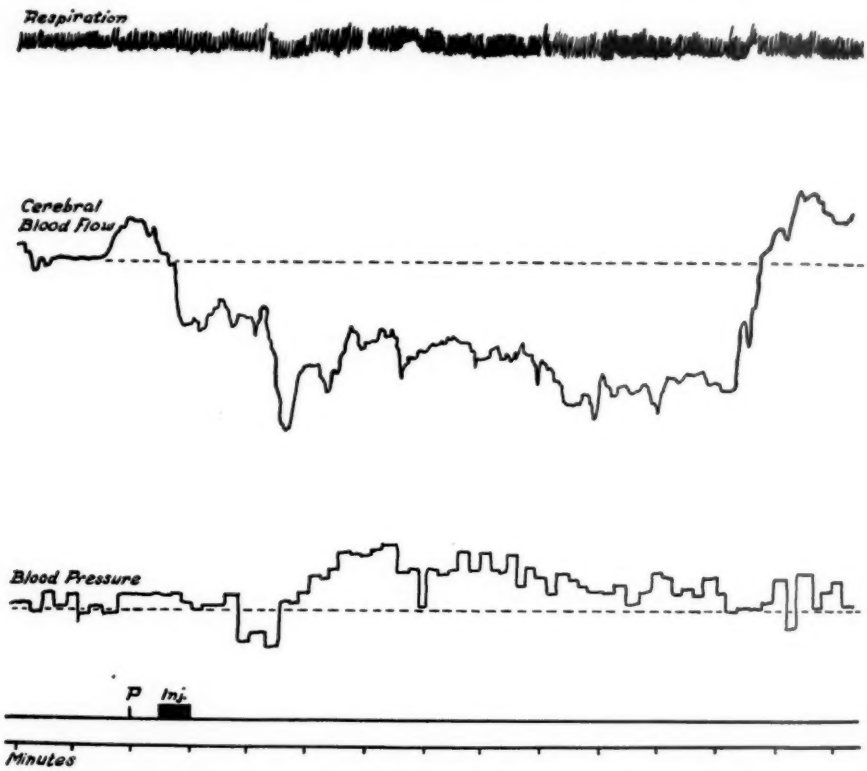

Fig. 2.—Effect of caffein on cerebral blood flow.

The curves have the significance as in Fig. 1. At *P* the needle was inserted into an arm vein. During period marked "Inj.," 0.5 gm. of caffein sodium benzoate was injected into blood stream. The maximum increase in blood pressure from the preinjection level was 33 mm. Hg.

haps, to the alkalosis induced by the stimulation of respiration. These findings are not in full accord with the experimental results in animals referred to above, but they are in accord with the indirect evidence on man obtained by other authors.

The beneficial effects of caffein in Cheyne-Stokes breathing cannot be explained by an improved circulation, unless it is assumed that increased flow occurs in only a certain small portion of the brain. If

circulation alone were responsible for clinical improvement from the use of caffein, yet greater benefit would be anticipated (but does not occur) from epinephrine.

AMYL NITRITE

The flushing of the skin and sharp drop in blood pressure which follow inhalation of amyl nitrite indicate a profound dilatation of arterioles. That this occurs also in cerebral vessels is proved by the throbbing sensation in the head, by the prompt rise in spinal fluid pressure of humans, and by the observed dilatation of pial arterioles of cats.[9] In the presence of both a dilatation of arterioles and a fall in systemic

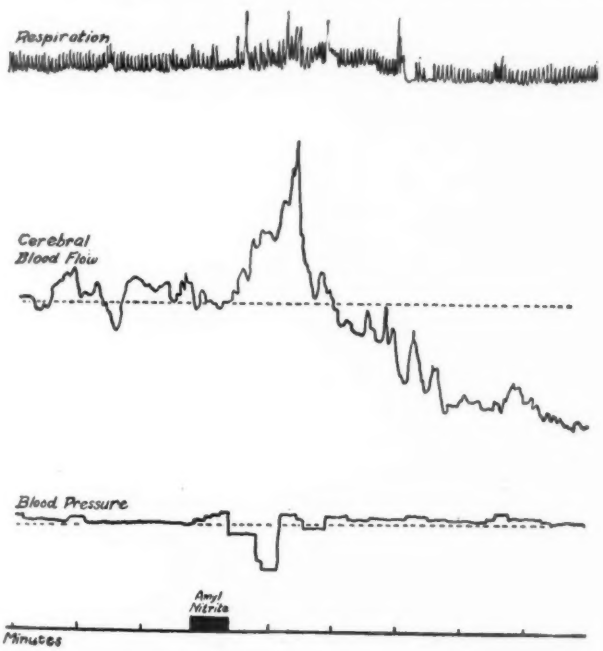

Fig. 3.—Effect of breathing amyl nitrite on cerebral blood flow.
Curves have the same significance as in Fig. 1. During the period marked "amyl nitrite," a crushed ampule was held under the subject's nose. The maximum decrease in blood pressure from the preinjection level was 25 mm. Hg.

blood pressure, whether the total blood flow through the brain increases or decreases can be told only by direct measurement.

In eight instances subjects inhaled the fumes from a crushed amyl nitrite pearl. They were instructed to breathe quietly in order not to introduce the factor of an altered CO_2 content of the blood. Inhalations were discontinued when the characteristic flushing of the face or drop in blood pressure appeared. The results as regards cerebral blood flow were varied. In four instances the blood flow increased, returning to its original level after several minutes. In two instances there was

a temporary rise, lasting less than a minute and followed by a fall. The happenings with respect to the blood pressure were constant: a drop occurred in all. In six of the eight cases the flow increased as the pressure fell, indicating a cerebral vasodilatation. A representative curve is that shown in Fig. 3.

In considering the effect of amyl nitrite and similar general vasodilators, it must be realized that the drop in blood pressure which they produce tends to reduce cerebral blood flow. The fact that there was, in six cases, an immediate increase in flow indicates that the cerebral vessels had dilated sufficiently to permit an increased flow despite the decrease in pressure. In the two cases in which a decrease in flow oc-

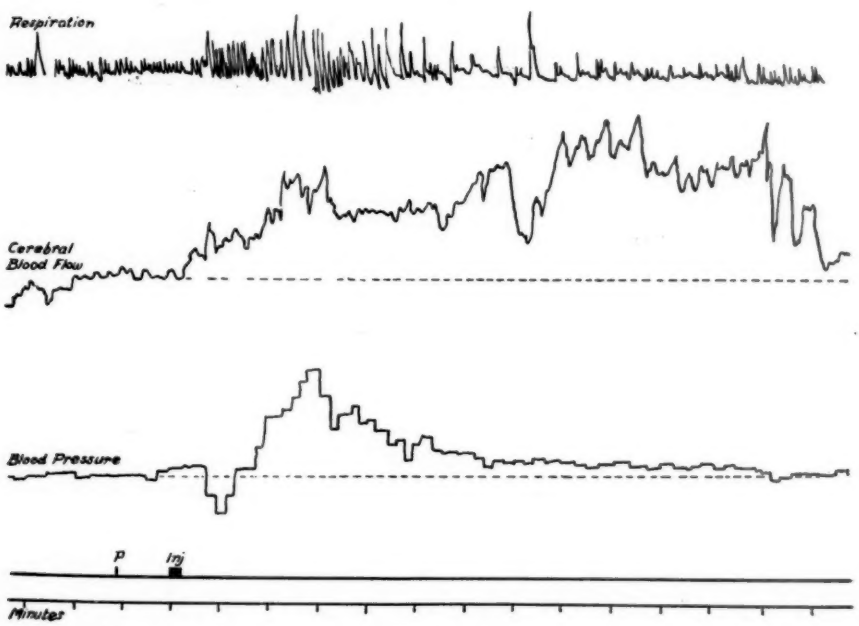

Fig. 4.—Effect of histamine on cerebral blood flow.

Tracings as in Fig. 1. At *P* needle was inserted into an arm vein. During period marked "Inj.," 0.5 mg. of histamine was injected into the blood stream. The maximum increase in blood pressure, above the preinjection level, was 25 mm. Hg.

curred, the cerebral vasodilatation presumably was not complete enough to compensate for the fall in pressure. In these two cases, however, the decrease in flow was not as great as would have been expected had so marked a drop in pressure occurred without an increase in the caliber of the cerebral vessels.

HISTAMINE

The difficulty of accepting animal experiments is shown by the diverse effects on pial vessels dependent on the type of anesthesia used.[10] With amytal anesthesia, injection of histamine caused pial dilatation. More important are the observations that intravenous injection of histamine,

because of the sharp increase in spinal fluid pressure, can be used in human subjects as a measure of circulation time from any vein to cerebral arterioles. Because there is not a corresponding fall in blood pressure, there must be a considerable increase in cerebral blood flow. Weiss and Lennox[11] found this to be true, judging from a decrease in the A-V difference for oxygen in the internal jugular vein blood.

In the single trial of histamine which we made, the result was as expected. The cerebral blood flow increased gradually but steadily for ten to fifteen minutes, then fell rather abruptly to the previous level. In contrast, the blood pressure first fell, then rose, and returned to the normal level while the flow was still increasing (Fig. 4).

SUMMARY

Records of changes in cerebral blood flow were obtained by means of a thermoelectric blood flow recorder introduced into the internal jugular vein of unanesthetized subjects. Simultaneous records were also made of respiration and blood pressure.

Intravenous injection of amounts of adrenalin chloride, sufficient to cause a marked rise in blood pressure, caused a great increase in cerebral blood flow, this increase undoubtedly being secondary to increase in blood pressure. Minute amounts of adrenalin caused a slight rise in flow without change (or with a fall) in blood pressure, suggesting a vasodilator action.

Intravenous injection of caffein sodium benzoate usually caused a decrease in flow, with eventual restoration to a normal or slightly more than normal level. Since this occurred in the face of an invariable rise in blood pressure, a temporary constricting action, perhaps secondary to respiratory stimulation, is indicated.

Inhalation of amyl nitrite produced usually an increase in flow in spite of a decrease in blood pressure, indicating a pronounced dilatation of cerebral vessels.

Intravenous injection of histamine in one case caused a gradual but progressive increase in blood flow, independent of blood pressure changes.

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THE PRECORDIAL ELECTROCARDIOGRAM

I. The Potential Variations of the Precordium and of the Extremities in Normal Subjects*

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Franklin D. Johnston, M.D., Ann Arbor, Mich.

IN A recent publication from this laboratory[1] a method of obtaining electrocardiograms which represent the potential variations of a single electrode was described. It was shown that a central terminal connected through large and equal resistances to the right arm, the left arm, and the left leg may be regarded as at zero potential throughout the cardiac cycle. When this terminal is paired with an exploring electrode, the curve obtained represents the potential variations produced by the heartbeat at any point with which this electrode is in contact. It is the purpose of this article to describe the curves obtained in a series of normal subjects by leading in this manner from the extremities and from a series of precordial points. An account of the curves obtained in the same way when ventricular hypertrophy or some other type of cardiac abnormality is present will be given in subsequent papers.

The normal precordial electrocardiogram has been studied in some detail by a number of previous investigators.[2-8] All of these have employed precordial leads of the kind introduced by Wolferth and Wood,[2] and the majority have taken leads from a single precordial point. The data which they have collected do not furnish adequate normal standards for the study of abnormal hearts by the method we have used. This study was carried out for the purpose of obtaining such standards.

METHODS

Thirty normal men (medical students) varying in age from twenty to thirty-five years were selected for this study. None of these had ever had symptoms referable to the heart, and none exhibited physical or roentgenographic signs of cardiac abnormality. Teleroentgenograms of the heart and lungs, made by the University Health Service, were available in all cases.† All electrocardiograms were made with the subject in the supine position. Two string galvanometers recording simultaneously on the same film were employed. One of these galvanometers was used in the ordinary way; the other was connected to the balanced plate circuit of a single-stage, vacuum-tube amplifier. The former was used to take standard Lead I simultaneously with each of a series of twelve curves recorded by the latter. The

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†In twenty-five cases the roentgenograms were taken either shortly after or less than ten months before the electrocardiographic study. In the remainder, with one exception, the interval between the electrocardiographic and the roentgenographic examination was less than two years.

first three curves of this series were standard Leads I, II, and III. The second three curves were obtained by pairing the indifferent central terminal with the electrodes on the right arm, left arm, and left leg in succession; these curves will be referred to as extremity potentials and will be designated by V_R, V_L, and V_F, respectively. The last six curves were obtained by pairing the central terminal with an exploring electrode placed in contact with the following precordial points: the fifth rib at the right sternal edge; the fifth rib at the left sternal edge; the fifth intercostal space midway between the left sternal edge and the left midclavicular line; the fifth intercostal space in the left midclavicular line; the sixth rib in the left anterior axillary line; and the tip of the ensiform process. The curves so obtained will be designated by the symbols V_1, V_2, V_3, V_4, V_5, and V_6, respectively. In taking those leads which represent the potential variations of a single point, the connections were so made that relative negativity of the electrode paired with the central terminal produced an upward deflection in the finished record. In the precordial curves a deflection of 1 cm. represents a potential difference of 2 millivolts; all other curves were taken with the galvanometer at normal sensitivity.

The contact surface of the electrode used in taking the precordial leads was roughly circular, and approximately 1 cm. in diameter; this electrode consisted of a small piece of sponge soaked in a strong solution of sodium chloride and thrust into the lower end of a glass tube where it came in contact with a small zinc plate. The skin of the precordium was prepared by vigorously rubbing it with a pad moistened with propanol until erythema appeared. The electrode was held in contact with the skin at the desired point by an assistant.

In six instances the precordial points at which the exploring electrode was placed were marked with small squares of metal held in place with adhesive tape, and a teleroentgenogram was taken with the subject in the supine position (Fig. 1).

THE STANDARD ELECTROCARDIOGRAMS AND EXTREMITY POTENTIALS

Judged by the criteria in general use, the majority of the standard electrocardiograms are well within normal limits. One subject displayed a QRS interval which measured 0.103 second. Another showed a grade of left axis deviation rarely seen in normal subjects; in this instance the index determined by the method of White and Bock[9] was 21.5, and the electrical axis determined by the method of Carter, Richter, and Greene[10] made an angle of −22 degrees with the horizontal. The S deflection measured 0.8 mv. in Lead II and 1.3 mv. in Lead III. In eight other electrocardiograms the voltage of R or S, and in one instance the voltage of T, was outside the normal limits established by Lewis and Gilder,[11] but R exceeded 2.0 mv. in only two instances. The minimum, maximum, and mean voltages of the Q, R, S, and T deflections are given in Table I. This table also gives in each instance the standard deviation and the coefficient of variation, which expresses the standard deviation as a percentage of the mean. The standard deviation is a measure of absolute variability, the coefficient of variation a measure of variability in relation to the magnitude of the mean.

The extremity leads V_R, V_L, and V_F were taken in such a way that a positive variation in potential is represented by a downward, a nega-

tive variation by an upward excursion of the string shadow. As in the case of the precordial leads, the individual deflections have, however, been labelled as if their directions were reversed; i.e., an initial summit is called Q, the inverted peak is called R, and the summit which follows R is called S. Our reasons for adopting this nomenclature are given in a subsequent paragraph. The extremity leads form a connecting link between the standard leads, to which they are closely and directly related,[1] and the precordial leads. For comparison with the latter they are much more useful than the standard leads because each represents the potential variations of a single extremity.

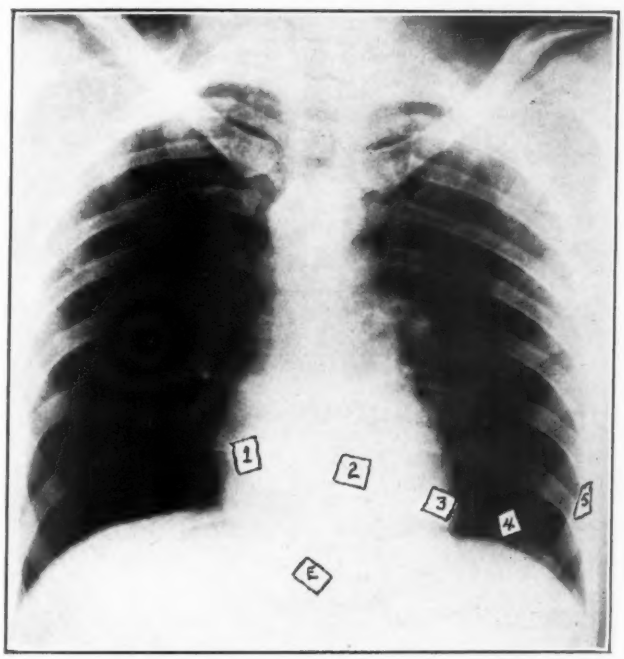

Fig. 1.—Teleroentgenogram of Subject 24 with metal markers on chest wall to show points from which precordial leads were taken. The time of onset of the chief upstroke (RS deflection) in seconds after the earliest QRS deflection in standard Lead I was: V_1, 0.033; V_2, 0.026; V_3, 0.049; V_4, 0.049; V_5, 0.044; V_E 0.027.

Their chief value lies in the relations which they often bring to light between the deflections of the standard leads and the corresponding deflections of the precordial leads.

In the majority of instances the ventricular complexes of the right arm lead begin with a prominent upright or negative deflection (labelled Q in Figs. 2 and 3 and in Table I). In this respect they differ from those obtained from the precordium. An initial downward or positive deflection is present in less than one-half the cases. The frequency with which this deflection is absent is probably due to the circumstance that the attachment of the right arm to the trunk lies

opposite the large valvular orifices at the base of the heart, so that the right arm displays variations in potential similar to those that occur in the ventricular cavities.

In normal subjects the QRS deflections of the left arm are ordinarily very small. The algebraic sum of the largest negative and the largest positive deflection in this lead may be taken as an index of the grade

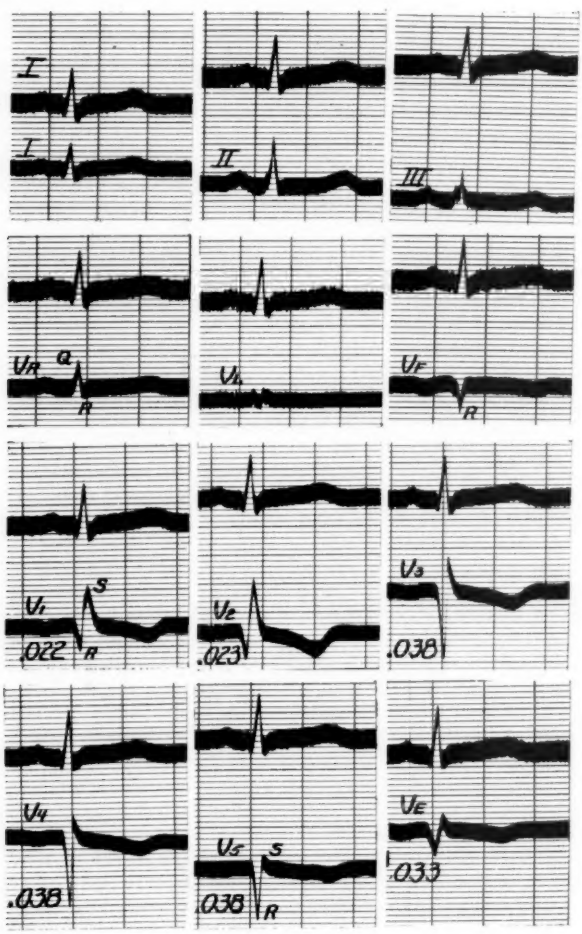

Fig. 2.—Standard leads (I, II, and III), extremity potentials (V_R, V_L, and V_F), and precordial potentials (V_1, V_2, V_3, V_4, V_5 and V_E) of Subject 19 taken simultaneously with standard Lead I (upper string in all curves). Extremity and precordial curves are labelled as if inverted. Time of onset of chief upstroke (RS deflection) is written on each of the six precordial curves. The latter were taken with the string at half the normal sensitivity (1 millivolt=2 cm.). In taking all other curves the string was at the normal sensitivity.

and kind of axis deviation shown by the standard leads. When multiplied by three, the index so obtained closely approaches in value that advocated by White and Bock.[9] Since the deflection in the left arm lead is at all times equal to one-third the deflection in Lead I minus

the deflection in Lead III, the reason is obvious. In our series of cases the average index determined by the method of White and Bock was 2.16; the average index determined from the left arm lead by the method described was 1.84. The largest discrepancy between the two methods encountered amounted to 4.1 units (0.41 mv.).

In general outline the ventricular complexes of the left leg lead usually resemble those inscribed in leads from the left side of the

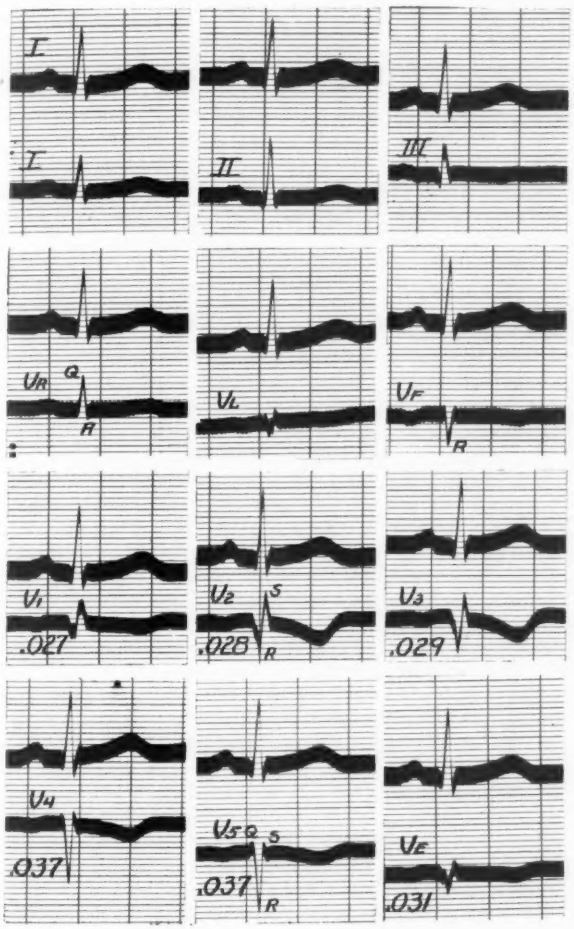

Fig. 3.—The standard leads (I, II and III) extremity potentials (V_R, V_L and V_F) and precordial potentials (V_1, V_2, V_3, V_4, V_5, and V_E) and Subject 4 taken simultaneously with standard Lead I. The figures written on the records give the time of the chief upstroke (RS deflection) with reference to the beginning of the earliest ventricular deflection in Lead I. The precordial curves were taken with the string at half the normal sensitivity; the remaining curves with the string at the normal sensitivity.

precordium (V_4 and V_5). When the electrical axis points toward the left leg, the resemblance is much closer than when the axis is more horizontal. When the standard leads display a conspicuous grade of left axis deviation, as in one of our subjects, the complexes of the leg

curve are similar to those obtained from the right side of the precordium, and the complexes of the left arm curve are like those obtained from the left side of the precordium.

The minimum, maximum, and mean values of the Q, R, S, and T deflections of the right arm, left arm, and left leg leads (V_R, V_L, and V_F) are given in Table I. In order to obtain a measure of the resemblance between the left leg curve and the curves obtained from the left side of the precordium, the coefficients of correlation between the amplitude of each of the QRS deflections in lead V_F and the amplitude of the corresponding deflection in lead V_5 were determined. For Q this coefficient was 0.518 ± 0.09; for R, 0.428 ± 0.1; and for S, 0.487 ± 0.094.* While these coefficients do not indicate a high degree of correlation, they show that there is a definite similarity between the QRS deflections of these two leads.

THE PRECORDIAL ELECTROCARDIOGRAM

In studying the precordial electrocardiograms we have confined our attention to the form of the ventricular complex. For the purposes of measuring the P-R and QRS intervals and of investigating the form of the auricular complex, precordial leads do not appear to be more useful than the standard leads.

In general outline the ventricular complexes of precordial leads closely resemble those obtained when the exploring electrode is placed directly in contact with the exposed ventricular surface. In normal curves the QRS group always displays a conspicuous downward movement followed by a sudden upstroke, which ordinarily carries the string shadow beyond the baseline. It has been pointed out that this sudden upstroke, which is produced by a large negative variation of the potential of the exploring electrode, corresponds to the intrinsic deflection of direct leads. It signals the arrival of the excitatory process at the epicardial surface of that portion of the ventricular wall which lies beneath the exploring electrode.

In normal curves from the right side of the precordium the chief upstroke occurs early in the QRS interval and usually rises high above the baseline. The downward deflection which precedes it is relatively small. In normal curves from the left side of the precordium the chief upstroke occurs relatively late in the QRS interval and may or may not rise above the baseline. The downward deflection is relatively large and is not infrequently preceded by a small initial summit.

The QRS group of a normal precordial electrocardiogram may, therefore, display three distinct apices; a preliminary summit, an inverted peak which marks the onset of the chief upstroke, and a final

*The correlation coefficient is a pure number which varies from +1 to −1. When the relation between two variables is perfect and positive, its value is +1. When the relation is perfect but inverse, its value is −1. For calculation of the probable error of the correlation coefficient see final note.

summit which marks the termination of the chief upstroke. The inverted peak is always present, but either or both summits may be absent. Slurring or slight notching of the chief deflections is not uncommon.

For the sake of convenience in description it is desirable that the different deflections inscribed during the QRS interval in precordial leads be designated by letters in the same manner as is customary in the case of the QRS deflections of the standard leads. The use of the letters Q, R, and S for this purpose has certain disadvantages but is, so it seems to us, preferable to the introduction of an entirely new terminology. Since the individual QRS deflections of standard leads do not originate in exactly the same way, and do not necessarily correspond to those of precordial leads either in number or in time, any method of assigning names to the latter must be arbitrary. The method adopted should, if possible, be applicable to abnormal, as well as to normal, curves.

In precordial curves the inverted peak which marks the onset of the chief upstroke is the most constant deflection of the QRS group. Since it corresponds in origin to the intrinsic deflection of direct leads, its recognition is of great importance. In the case of the standard leads it is customary to label a downward deflection "S" when it is preceded by an upward deflection, and "Q" when it is not. If we follow the same plan in labeling precordial curves, the name given to the deflection in question will depend upon whether it is or is not preceded by a small initial summit. Since, however, its origin and its significance are the same in either case, we believe that it should always be designated by the same symbol. We advocate calling this deflection "R," and naming the summit which usually follows it "S." The summit which sometimes precedes it may then be called "Q." In justification of this proposal a few words of explanation are desirable. Some investigators, Groedel[12] for instance, have taken precordial curves in such a way that relative negativity of the exploring electrode is represented in the finished record by a downward instead of by an upward deflection. In comparison with the one we have used this method reverses the direction of all the deflections. It has a number of decided advantages, and it is not unlikely that it will eventually come into general use. It yields precordial curves in which P and T are normally upright, instead of inverted, and in which the QRS deflections also are very similar in general outline to those of the standard leads. It has the further advantage that negativity of the exploring electrode is represented by a downward deflection, positivity of this electrode by an upward deflection—an arrangement which is more conventional than the reverse and which makes it possible to refer to downward deflections as negative and upward deflections as positive without danger of being misunderstood. As we have

already indicated, it greatly simplifies the problem of naming the QRS deflections of normal precordial curves, and permits us to use the letters Q, R, and S in exactly the same manner as in the case of the standard leads.

The method of taking precordial leads which we have used was originally adopted in this laboratory in order to emphasize the similarity in form between human precordial curves and the ventricular complexes of the direct leads employed in animal experiments by Lewis and Rothschild.[13] These were so taken that the intrinsic deflection was represented by an upstroke. The advantages of reversing the polarity of all direct, semidirect, and precordial leads are, however, so great that we believe this policy will eventually be adopted by the majority. For this reason and in order to avoid introducing a new nomenclature, we have labelled the precordial curves of this article as if they were inverted. It seems to us desirable that the individual deflections of the ventricular complex in precordial leads be designated by the same letters by all workers, regardless of whether the left- or the right-hand electrode is placed in contact with the precordium.

THE VOLTAGE OF THE VENTRICULAR DEFLECTIONS IN PRECORDIAL LEADS

The minimum, maximum, and mean voltages of Q, R, S, and T in the precordial leads employed are shown in Table I. An initial summit or Q reflection did not occur in the ensiform lead (V_E) or in either of the first two precordial leads (V_1 and V_2) in a single instance. In the third precordial lead (V_3) such a deflection was present only once, but in the fourth precordial lead (V_4) it occurred ten times and in the fifth precordial lead (V_5), eleven times. The magnitude of the chief deflections, R and S, showed a sort of reciprocal relationship; as the exploring electrode was moved over the precordium from right to left the former tended to become larger, the latter smaller. The average voltage of the R deflection (Table I) increased progressively in the first four precordial leads and was nearly as great in the fifth as in the fourth where it was maximal. On the other hand, the average voltage of the S deflection was nearly as great in the first precordial lead as in the second in which it reached its greatest value. In the leads taken farther to the left it progressively decreased. In the leads from the left side of the precordium this deflection was sometimes absent; three times in the third lead, four times in the fourth, and twelve times in the fifth. In the ensiform lead it was absent twice.

The chief upstroke in precordial leads begins at the apex of R and ends at the apex of S. Its amplitude may be measured directly or may be found by adding (without regard to sign) the voltages of these two deflections. The figure so obtained gives a better idea of the magnitude of the potential variations produced by the heartbeat in a given lead than does the voltage of the largest QRS deflection meas-

TABLE I

THE SIZE OF THE VENTRICULAR DEFLECTIONS IN THE STANDARD AND SPECIAL LEADS (MEASUREMENTS GIVEN IN TENTHS OF A MILLIVOLT)

	Q					R					S					T					RS				
LEAD	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	COEFF. VARIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	COEFF. VARIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	COEFF. VARIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	COEFF. VARIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	COEFF. VARIATION
I	0	1.5	0.33	0.45	135.1	1.5	19.4	6.81	3.27	48.0	0	5.0	1.67	1.35	81.1	1.0	5.5	2.21	1.05	47.5	3.0	20.6	8.63	3.20	37.1
II	0	2.0	0.43	0.61	140.1	4.0	22.0	11.99	4.39	36.6	0	8.0	1.53	1.92	125.7	1.0	6.0	2.97	1.10	37.0	8.0	23.0	13.76	3.72	27.1
III	0	2.0	0.54	0.60	111.7	1.2	18.0	8.50	4.33	50.9	0	13.0	1.27	2.40	189.1	0	3.0	1.49	0.75	50.4	3.2	18.0	10.12	4.10	40.5
V_R	0	7.6	2.81	2.68	95.7	0	3.0	0.76	0.65	85.0	0	10.5	2.56	3.41	136.5	−3.3	−0.8	−1.66	0.61	36.7	3.5	11.7	6.30	1.82	28.9
V_L	0	1.5	0.21	0.42	195.4	0	7.0	1.13	1.34	118.4	0	7.0	2.00	1.60	80.3	-1.0	1.0	0.05	0.41	825.2	0.5	8.5	3.27	1.85	56.7
V_F	0	1.2	0.29	0.37	127.2	0	13.0	6.68	2.81	42.1	0	6.5	0.80	1.28	160.5	0.2	2.8	1.46	0.62	42.1	4.0	13.0	7.66	2.54	33.2
V_1	0	0	0	0		1.0	9.6	4.16	2.33	56.0	3.4	24.0	11.05	5.03	45.5	-4.0	5.6	1.23	1.88	152.9	6.6	26.8	15.21	5.98	39.2
V_2	0	0	0	0		4.0	20.8	9.05	3.68	40.6	3.0	38.8	16.23	7.30	45.0	2.4	11.0	6.22	1.90	30.6	15.0	46.0	25.27	7.47	29.6
V_3	0	0.4	0.013	0.072	538.6	6.0	54.6	16.70	9.78	58.6	0	22.0	9.05	5.62	62.1	3.6	12.0	6.26	1.89	30.2	12.6	54.6	25.75	8.37	32.5
V_4	0	3.0	0.37	0.68	185.8	12.2	46.0	22.31	7.10	31.8	0	16.0	5.32	4.13	77.6	2.4	11.0	5.66	1.84	32.6	18.0	51.6	27.63	6.71	24.1
V_5	0	3.4	0.57	0.91	161.0	8.8	33.0	18.78	6.91	36.8	0	9.6	1.93	2.22	115.2	2.0	9.6	4.59	1.82	39.7	11.2	33.2	20.70	6.50	31.4
V_E	0	0	0	0		2.0	12.8	5.81	2.49	42.8	0	16.2	6.09	4.78	78.4	0.2	5.2	2.55	1.11	43.5	5.6	24.2	11.91	4.33	36.4

ured from the baseline. When Q is larger than S, the QR downstroke is larger than the RS upstroke, but the difference is seldom great in normal subjects. The latter movement is more abrupt than the former and corresponds to the intrinsic deflection of direct leads. Whenever possible it has, therefore, seemed preferable to take the height of the chief upstroke rather than the amplitude of the largest excursion of the string, regardless of its direction, as a measure of the magnitude of the potential variations of the exploring electrode.

The minimum, maximum, and mean amplitude of the chief upstroke or RS deflection in the various leads employed are given in Table I. In the case of the standard leads and of the right- and left-arm leads a deflection strictly analogous to the intrinsic deflection of direct leads was frequently absent or could not be identified. In such cases the sum of the largest downward deflection and the largest upward deflection was substituted for the amplitude of the chief upstroke or RS deflection.

It will be seen that the RS deflection is on the average considerably larger in the second, third, and fourth precordial leads than in the first or fifth or the ensiform lead. For this difference several factors may be responsible, but we believe that the distance of the exploring electrode from the heart is the most important. There is a striking falling off in the amplitude of the ventricular deflections when the distance of this electrode from the heart is increased. For this reason the amplitude of the chief upstroke is three and one-half or four times as large in the midprecordial leads (V_2, V_3, and V_4) as in the extremity leads (V_R, V_L, and V_F) and two or two and one-half times as large as the largest excursions of the string seen in the standard leads. The large size of the RS deflection in the second, third, and fourth precordial lead is probably due, therefore, to the nearness of the exploring electrode to the heart's surface.

The question arises whether there is any relation between the amplitude of the QRS deflections in the precordial leads and the amplitude of these deflections in the standard leads. In order to answer this question, we have determined the coefficient which measures the correlation between the magnitude of the RS deflection in the fourth precordial lead and the greatest excursion of the string shadow (R plus S or R plus Q) in Lead II. For our series of cases this coefficient is 0.429 ± 0.1. We also determined the correlation coefficient for the largest RS deflection in any precordial lead paired with the largest excursion of the string in any standard lead; this coefficient is 0.458 ± 0.097. It seems, therefore, that the size of the QRS deflections in the standard leads and the size of these deflections in the precordial leads tend to vary in a parallel manner, but that no very close relation exists.

The junction of the last deflection of the QRS group with the final deflection of the ventricular complex (the S-T junction) usually occurred very close to the baseline, and the voltage that separated it from this line was never greater than 0.15 mv. This voltage was usually positive; it was negative in only eight instances. The portion of the ventricular complex lying between the S-T junction and the apex of T was sometimes represented by a straight line, but more often by a curve slightly convex toward the baseline.

In all precordial leads, except the first, the potential of the exploring electrode during the inscription of T was invariably positive, and, in our curves, this deflection was therefore downward. In the first precordial lead, however, T was upright in three instances. The average voltage of T was greatest in the second and third precordial leads (V_2 and V_3) and showed a progressive decrease in the leads taken farther to the left. It was smallest in the first lead (V_1). In tabulating measurements of the T deflection, T-waves which were upright in our curves were considered negative and inverted T-waves, positive; during the inscription of the former the potential of the exploring electrode was negative; during the inscription of the latter it was positive.

Whether the form of the ventricular complex is more variable in precordial than in the standard leads, or vice versa, is a question that is difficult to answer. We have attempted to obtain some exact information on this point by computing the standard deviations and the coefficients of variation of the amplitudes of the various deflections in each lead. The standard deviation or root-mean-square deviation from the mean is the standard measure of absolute variability, but it is not suitable for comparing the variability of quantities which differ widely in average magnitude or which are measured in different units. To overcome this difficulty statisticians introduced the coefficient of variation, which expresses the standard deviation as a percentage of the mean. It is supposed to measure relative variability and is a pure number, and, therefore, not dependent upon the unit of measurement. While it may be a satisfactory measure of relative variability under certain conditions, it is wholly unsatisfactory in the present circumstances.

It is obvious that when the variates may take negative as well as positive values, as in the case of the voltage of the T-wave in certain leads, the mean is likely to be absolutely small and may be zero. In the latter case the coefficient of variation becomes infinite, even though the standard deviation is small. A similar situation arises when a considerable number of the variates are zero. The Q deflection in the third precordial lead, for example, was absent in twenty-nine instances out of thirty. The mean amplitude of this deflection was, therefore, very small and the coefficient of variation, very large. We

would not ordinarily, however, think of a deflection which had the same value, in this case zero, in all but one instance as highly variable. In all those instances in which the minimum amplitude of the variate is zero or negative, the coefficient of variation must be regarded as practically meaningless for our present purpose. While its failure under these circumstances casts some doubt upon its value in the remaining instances, no more satisfactory measure of relative variability is available.

When the deflections of the precordial leads are compared with the corresponding deflections of the standard leads, it will be seen that the coefficients of variation are not, as a rule, materially larger in the one case than in the other. It should be noted that very bizarre QRS groups, such as are frequently seen in standard Lead III, rarely if ever occur in precordial leads in normal subjects.

For a few deflections we determined the third and fourth moments about the mean and computed the skewness and the excess or measure of kurtosis. The skewness of the distribution was positive in all instances, and it was sometimes large; the excess was sometimes negative, sometimes positive, and in the latter case occasionally very large. Because the number of variates in each array is only thirty, however, the statistical constants that depend upon the higher moments have a very large probable error. We concluded that the information to be gained from them would not justify the labor that computing them would require. It is clear that the difference between the mean and the maximum amplitude of a given electrocardiographic deflection is almost always considerably greater than the difference between the mean and the minimum amplitude.

TIME OF ONSET OF THE CHIEF UPSTROKE (RS DEFLECTION)

It has already been pointed out that the chief upstroke or RS deflection occurs earlier in leads from the right side of the precordium than in leads from the left side. The interval from the beginning of the earliest QRS deflection in Lead I to the onset of the chief upstroke in each precordial lead was carefully measured.* The minimum, maximum, and average values of this interval for each of the six precordial leads employed are given in Table II. The first QRS deflection of Lead I does not necessarily occur at the very beginning of the QRS interval, nor does it always occupy in different subjects exactly the same position in this interval. For this reason the values of the interval in question for the different precordial leads show a considerable degree of correlation, one with another. When the value of this interval in the first was paired with its value in the fifth precordial lead, the correlation coefficient was found to be 0.73 ± 0.057.

*The measuring machine devised by Captain Elliott and manufactured by the Cambridge Company was used for this purpose.

When the mean value of this interval in the first two precordial leads (V_1 and V_2) was paired with its mean value in the fourth and fifth, the correlation coefficient was 0.67 ± 0.069. It is clear, therefore, that the absolute magnitude of the figures given for the different leads are much less significant than their relative magnitude. The smallest difference in time between the earliest and the latest chief upstroke in the same subject measured 0.008 second; the largest, 0.03 second. This difference in time exceeded 0.025 second in only six instances; its mean value for our series of cases was 0.0194 second. On the average the chief upstroke began about 0.016 second earlier in the first two precordial leads than in the fourth and fifth (V_4 and V_5). The average figures for the two leads of the first pair are very much alike, and the same is true of the average figures for the two leads of the second pair. The average figure for the ensiform lead and that for the third precordial lead have an intermediate value, but the former is similar to the figures for the first and second precordial leads while the latter is similar to the figures for the fourth and fifth.

TABLE II

TIME OF ONSET OF THE CHIEF UPSTROKE (RS DEFLECTION) WITH REFERENCE TO THE EARLIEST VENTRICULAR DEFLECTION OF LEAD I

LEAD	MINIMUM SECONDS	MAXIMUM SECONDS	MEAN SECONDS	STANDARD DEVIATION SECONDS	COEFFICIENT OF VARIATION (PER CENT)
V_1	0.006	0.033	0.0172	0.0064	37.0
V_2	0.003	0.039	0.0193	0.0085	44.0
V_3	0.013	0.049	0.0314	0.0097	30.9
V_4	0.023	0.055	0.0349	0.0075	21.5
V_5	0.023	0.053	0.0336	0.0074	22.0
V_E	0.006	0.048	0.0249	0.0104	41.7
Difference between shortest and longest interval	0.008	0.030	0.0194	0.0057	29.4

The reason for this grouping apparently lies in the relation of the exploring electrode in its different positions to the anterior surfaces of the two ventricles. It has been pointed out in previous papers that the ventricular deflections of a given precordial lead are usually similar in general outline to those which would be inscribed in direct leads from that portion of the ventricular wall that lies beneath the exploring electrode. It would be anticipated that leads from the right side of the precordium would show an early chief upstroke corresponding to the early intrinsic deflection seen in direct leads from the ventral surface of the right ventricle and that leads from the left side of the precordium would show a late chief upstroke corresponding to the late intrinsic deflection seen in direct leads from the ventral surface of the left ventricle.

In taking a precordial lead defined by the landmarks of the anterior chest wall, the relation of the precordial electrode to the two ven-

tricles naturally varies from subject to subject. In six instances the points where this electrode was applied were marked by small pieces of metal fixed to the chest wall with adhesive tape, and a teleroentgenogram (Fig. 1) was taken with the subject in the supine position, in which the electrocardiographic study was made. It was found that minor errors in placing the electrodes were sometimes made so that they did not always bear exactly the same relation to the bones of the thoracic cage. For this reason and because of the differences between subjects with respect to the height of the diaphragm and the position of the heart, the relation of the metal markers to the boundaries of the cardiac shadow showed considerable variation. In five of the cases studied, the images of the markers corresponding to the ensiform lead and to the first three precordial leads were wholly or partly superimposed upon the cardiac silhouette. In one instance in which the heart shadow was vertically placed, the marker for the third precordial lead fell just outside its left margin. In the case of the subject who showed an unusual degree of left axis deviation, the marker for the fourth precordial lead was partly superimposed upon the shadow of the apex; in all other instances the fourth and fifth markers fell well outside the boundaries of the cardiac image. It is not possible accurately to mark the position of the atrioventricular or of the interventricular groove upon the cardiac silhouette. Nevertheless, the position of the markers with reference to the cardiac shadow suggests that in taking the first two precordial leads and the ensiform lead the exploring electrode was usually placed over the right ventricle. The fourth and fifth precordial leads and in most instances the third as well must be regarded as semidirect leads from the surface of the left ventricle. In taking the third precordial lead, more rarely in taking the second, the exploring electrode was undoubtedly sometimes placed approximately over the interventricular sulcus so that a semidirect lead from both ventricles was obtained.

An x-ray film which shows the relation of the markers to the cardiac silhouette in one of our subjects is reproduced in Fig. 1. The figures which define the position of the chief upstroke in each lead are given in the legend. In the first two precordial leads and in the ensiform lead this upstroke began approximately 0.03 second after the first ventricular deflection in Lead I, while in the last three precordial leads (V_3, V_4, and V_5) it began approximately 0.05 second later.

When the exploring electrode was moved over the precordium from right to left, the change from an early to a late chief upstroke was often abrupt. In twenty-three of the thirty subjects examined, the first late chief upstroke occurred in the third precordial lead; in two cases it occurred in the second and in five cases in the fourth. When the chief upstroke was distinctly notched, it was usually found that the notch was simultaneous or nearly simultaneous with the onset of the chief upstroke in leads taken farther to the left. Notches that

occurred before the onset of the chief upstroke were usually simultaneous with the onset of the chief upstroke in leads taken farther to the right. This suggests that, in precordial leads at least, notches are frequently produced by the difference in time between the activation of the right and the activation of the left ventricular surface.

TABLE III

LEAD	1 NUMBER OF CASES IN WHICH FIRST LATE CHIEF UPSTROKE OCCURRED	2 NUMBER OF CASES IN WHICH R FIRST EXCEEDED S	3 NUMBER OF CASES IN WHICH CHIEF UPSTROKE WAS MAXIMAL	4 SIMULTANEOUS OCCURRENCE OF FEATURES IN COLUMNS 1 AND 2	5 SIMULTANEOUS OCCURRENCE OF FEATURES IN COLUMNS 1 AND 3	6 SIMULTANEOUS OCCURRENCE OF FEATURES IN COLUMNS 2 AND 3	7 SIMULTANEOUS OCCURRENCE OF FEATURES IN COLUMNS 1, 2, AND 3
V_1	0	1	0	0	0	0	0
V_2	2	3	7	1	0	0	0
V_3	23	18	8	16	8	7	6
V_4	5	7	12	4	1	2	1
V_5	0	1	3	0	0	0	0
V_E	0	(omitted)	0	--	0	-	-
Totals	30	30	30	21	9	9	7

In Table III the first column gives the number of times each precordial lead was the lead farthest to the right in which the chief upstroke occurred late and approximately at the same time as in leads taken more to the left. The second column gives the number of times that each lead was the lead farthest to the right in which the positive deflection R was larger than the negative deflection S. The ensiform lead is here omitted from consideration. In normal subjects this lead is not a particularly favorable one; the QRS deflections are usually small, and in many instances R is larger than S when the opposite is true in other leads from the right side of the precordium. The third column gives the number of instances in which the chief upstroke reached its maximal amplitude in each lead. The last four columns show the number of instances in which each two and all three of the characteristics in question occurred together in each lead. It will be seen that there was a definite tendency for the first late upstroke to occur in the first lead in which R was larger than S, but no particular tendency for the first late chief upstroke to exceed the others in amplitude.

SUMMARY

Using a method which makes it possible to obtain electrocardiograms that represent the potential variations of a single electrode, a study of thirty normal subjects was carried out. The three standard leads and nine special leads were each taken simultaneously with Lead I. Three of the special leads recorded the potential variations of the right arm, left arm, and left leg, respectively; the others recorded the potential variations of a series of six precordial points.

The special curves were taken in such a way that negativity of the exploring electrode, placed upon one of the extremities or upon the precordium, produced an upward deflection in the completed record. It is, however, pointed out that several advantages might be gained by making the connections in the opposite way. For this reason, and to avoid introducing a new nomenclature, our special leads have been labelled as if the direction of the deflections were reversed.

In precordial leads the QRS group may normally show three distinct apices, which for convenience in description may be called "Q," "R," and "S." The R peak, which represents a positive variation in the potential of the exploring electrode and is therefore inverted in our records, is always present. This peak marks the beginning of a large and rapid excursion of the string which corresponds to the intrinsic deflection of direct leads from the ventricular surface. In leads from the right side of the precordium R is smaller and, on the average, reaches its apex about 0.02 second earlier than in leads from the left side. This indicates that, as a whole, the epicardial surface of the ventral wall of the right ventricle is activated earlier than the corresponding surface of the left.

In our records Q and S are both summits. The former is always small in normal subjects and occurs only in leads from the left side of the precordium. The latter is larger on the right side of the precordium than on the left where it may be absent. When the exploring electrode is placed at or to the left of the sternal edge, its potential is invariably positive during the inscription of the T deflection. When the exploring electrode is placed to the right of the midline, the direction of T is variable.

The leads which represent the potential variations of the extremities are related both to the standard leads and to precordial leads and are useful in comparing the one with the other. When the standard leads are of the normal type, the left leg curve usually resembles those obtained from the left side of the precordium, and the deflections of the left arm curve are small.

The authors wish to express their appreciation to Dr. Frank N. Wilson for his help, particularly in the preparation of the paper.

NOTE.—The probable errors of the correlation coefficients given in this article were obtained by application of the formula

$$\text{P.E.}_r = \pm 0.6745 \frac{1 - r^2}{\sqrt{N}}$$

in which N is number of variates and r the coefficient of correlation. In the present instance N equals 30. The probable error of the mean values given may be obtained by the formula

$$\text{P.E. of mean} = \pm \frac{0.6745\ \sigma}{\sqrt{N}}$$

in which σ is the standard deviation.

(See Pearl, *Medical Biometry and Statistics,* ed. 2, Philadelphia, 1930, W. B. Saunders Co.)

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ELECTROCARDIOGRAPHIC ABNORMALITIES CHARACTERISTIC OF CERTAIN CASES OF ARTERIAL HYPERTENSION*

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IN THE course of an investigation into the serial electrocardiographic changes following upon acute coronary occlusion, one of us (H. E. R.) found a number of cases showing abnormalities of the ventricular complexes (QRST) of an unusual type. In certain respects the abnormalities observed in the records of these cases simulated, and in other respects differed from the typical electrocardiographic changes found in myocardial infarction. Further, it was found that without exception all of these atypical records showed an identical type of electrocardiographic abnormality. On examining the histories of this small group of patients, it appeared that a diagnosis of coronary thrombosis had, in each case, been made largely on this electrocardiographic abnormality and that the clinical histories, while in some cases suggestive, in practically all gave but inconclusive support to that diagnosis. Attention was further attracted to these patients when it was observed that all had arterial hypertension at the time when these electrocardiographic records were made. In view of these observations, it seemed desirable to differentiate the electrocardiographic changes observed from the typical changes of coronary thrombosis and also to determine by means of clinical study the nature of the relationship, if any, of the electrocardiographic changes to coronary thrombosis and to arterial hypertension.

CHANGES OF VENTRICULAR COMPLEX

In Figs. 1 to 10, electrocardiograms of the type to be discussed are shown. These records which exhibit almost identical features were obtained from ten different patients who were selected at random from the 143 cases upon which the clinical study is based. The distinctive features of these curves may be described as follows:

The T-wave in the first lead is always a negative deflection and is of the so-called coronary type, being shouldered and having a sharp apex angle. In the third lead the T-wave invariably presents the reverse appearance to that of T_1: it is always a positive deflection, and in the majority of our records the amplitude of T_3 is abnormally in-

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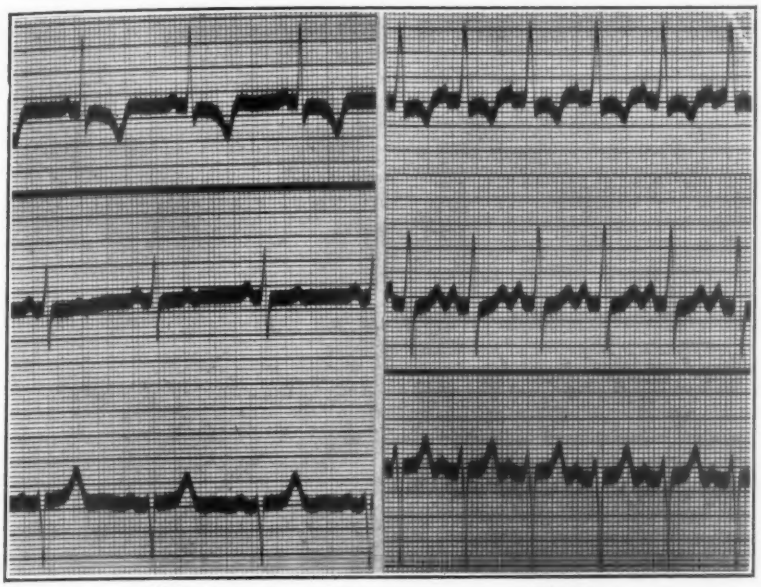

Fig. 1. Fig. 2.

Fig. 1.—Case 26. Three usual leads. Blood pressure 180/110. Diagnosis: chronic myocarditis, degenerative; angina pectoris; cardiac hypertrophy.

Fig. 2.—Case 85. Leads I, II, and III. Blood pressure 260/140. Diagnosis: malignant hypertension; chronic myocarditis, degenerative; cardiac hypertrophy.

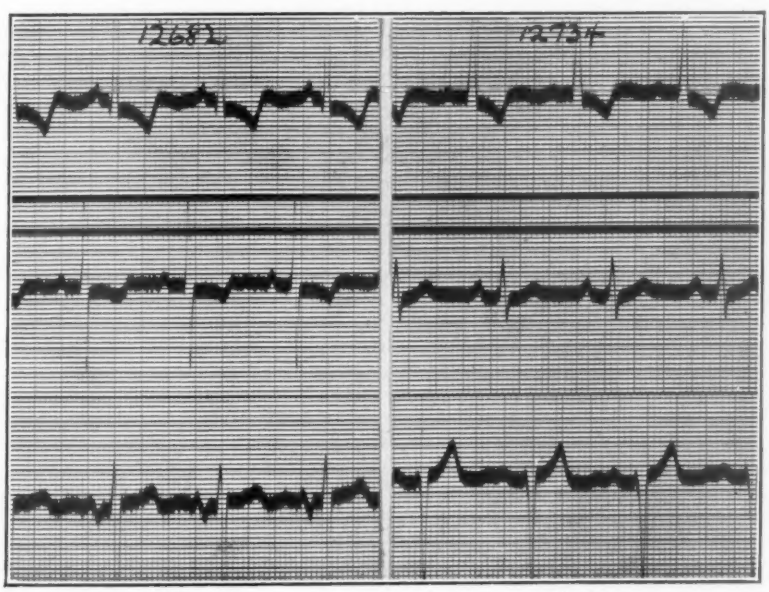

Fig. 3. Fig. 4.

Fig. 3.—Case 135. Blood pressure 216/120. Diagnosis: chronic myocarditis, degenerative; cardiac hypertrophy; cardiac insufficiency.

Fig. 4.—Case 139. Blood pressure 224/128. Diagnosis: chronic myocarditis, degenerative; cardiac hypertrophy; chronic nephritis.

creased. The T-wave in Lead II may be a positive, diphasic, or negative deflection. When negative, T_2 may resemble T_1 in contour.

In addition to the T-wave abnormalities, these records show a characteristic type of alteration of that segment of the isoelectric line which lies between the R- or S-waves and the T-wave—the RT or ST segment. In Lead I the RT segment in this type of record is constantly displaced below the level of the isoelectric line. This displacement is not less than 1 mm. and is seldom greater than 2.5 mm. It is never so marked as may be the early RT deviation in the typical T_1 or T_3 type of tracings of coronary thrombosis. In the third lead the RT or ST interval is, in the

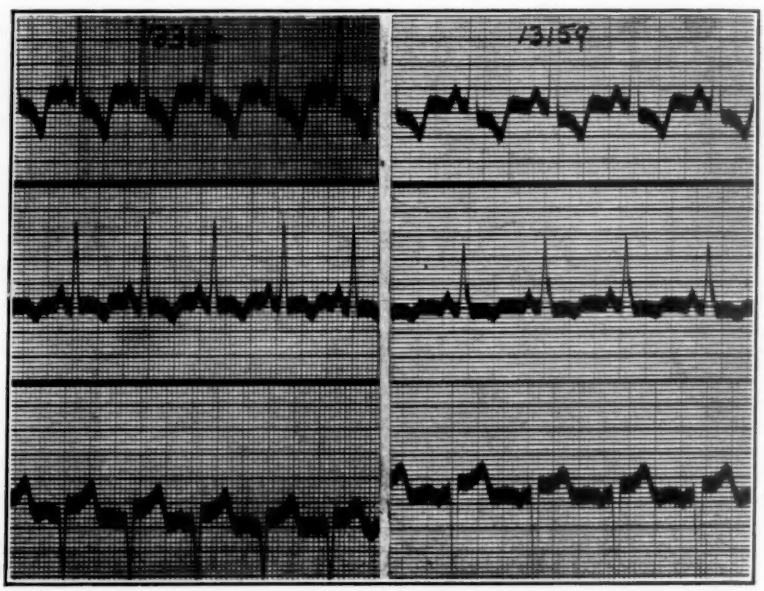

Fig. 5. Fig. 6.

Fig. 5.—Case 29. Blood pressure 206/120. Diagnosis: chronic myocarditis, degenerative; cardiac hypertrophy; angina pectoris.

Fig. 6.—Case 84. Usual leads. Blood pressure 240/140, 190/140. Diagnosis: malignant hypertension; chronic myocarditis, degenerative; cardiac hypertrophy; hemiplegia.

majority of records, elevated above the isoelectric potential. Rarely, however, as in Figs. 1 and 2, the RT segment in the third lead may appear to be almost isoelectric. In Lead II the RT interval may be isoelectric or may exhibit a variable abnormality. Abnormal left axis deviation of marked degree is present in all records of this type. The maximum positive deflection occurs in the first, and the maximum negative deflection in the third lead of these electrocardiograms. In the greater number of these records the voltage of the QRS complexes in Leads I and III was materially increased, and in none was a voltage of less than 1 millivolt observed.

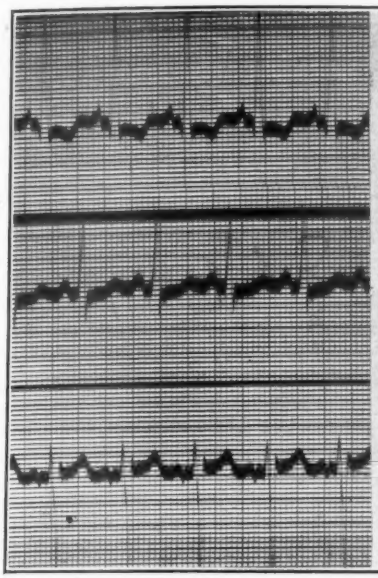

Fig. 7.

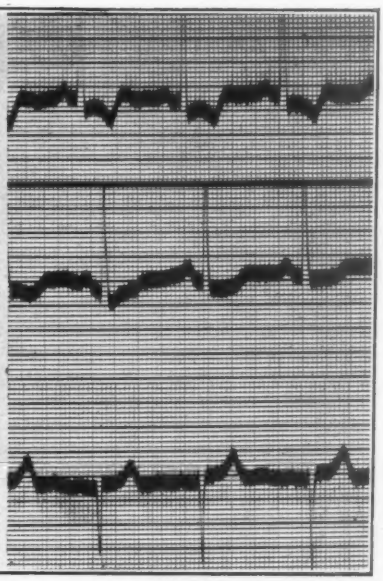

Fig. 8.

Fig. 7.—Case 7. Blood pressure 180/110. Diagnosis: chronic nephritis; chronic myocarditis, degenerative; cardiac hypertrophy; uremia.

Fig. 8.—Case 129. Blood pressure 280/116. Diagnosis: intermittent claudication; cardiac hypertrophy; chronic myocarditis, degenerative.

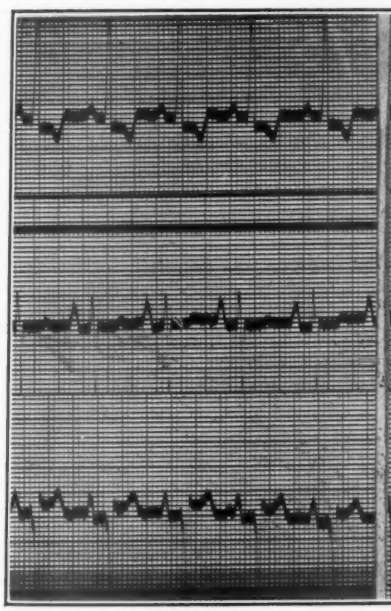

Fig. 9.

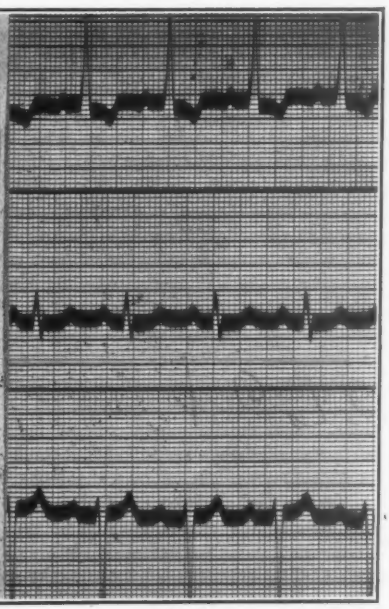

Fig. 10.

Fig. 9.—Case 80. Blood pressure 194/110. Showing changes similar to Figs. 1-8, occurring in a patient who had coronary thrombosis one week before this record was taken. Subsequent serial electrocardiogram showed no significant alteration of the ventricular complexes.

Fig. 10.—Leads I, II, and III, showing similar type of change in a patient with normal blood pressure who had sclerotic aortic stenosis. Electrocardiograms of this type were rarely observed in the absence of hypertension.

Intraventricular conduction time, as estimated by the width of the QRS base, never measures more than 0.10 second and in most electrocardiograms measures less than 0.08 second. Intraventricular conduction defects, therefore, can be definitely excluded, and the presence in these records of abnormal RT deviation and T-wave deflection cannot be explained on the basis of a branch-bundle lesion.

COMPARISON OF ELECTROCARDIOGRAMS SHOWING CHANGES DESCRIBED WITH TYPICAL ELECTROCARDIOGRAMS OF MYOCARDIAL INFARCTION

The three electrocardiograms shown in Fig. 11A were obtained from a patient who had arterial hypertension, degenerative heart disease, and intermittent claudication. The first of these three electrocardiograms was taken upon the entry of the patient into hospital; the second was taken two months later; and the third two years later. These three records are identical and present the abnormal features under discussion. The electrocardiograms in Fig. 11B were taken from a patient who had the typical clinical syndrome of acute coronary occlusion. They present the characteristic electrocardiographic abnormalities of coronary thrombosis of the T_1 type. These records were obtained three hours, ten days, and three months, respectively, after the onset of the substernal pain. Upon comparing these two series of records (Figs. 11A and 11B), it will be observed that the late T-wave changes in coronary thrombosis simulate in certain respects the T-wave changes in the records from the hypertension patient. In both, the T-wave in Lead I is a sharply negative, shouldered deflection, while in Lead III the T-wave is a positive deflection of increased amplitude. In other respects, however, these two series of electrocardiograms are entirely dissimilar. Although taken at intervals of many months, the records obtained from the hypertension patient show no significant alteration of the ventricular complexes. In this regard these three electrocardiograms (Fig. 11A) differ markedly from those obtained from the patient who had myocardial infarction. The latter are characterized by the occurrence of a rapid sequence of changes in the ventricular complexes (QRST). The RS-T displacement in these, as in the typical early records of coronary thrombosis is an evanescent abnormality. As was demonstrated by Parkinson and Bedford,[1] the displacement of the RS-T segment may occur within a few hours of myocardial infarction. This may persist for a variable period, but in the average case the RT interval returns to isoelectric potential within fourteen to twenty-one days. In this respect the electrocardiograms of myocardial infarction are entirely unlike those derived from our series of hypertensive patients. As may be observed from Fig. 11A, the RS-T change which was present in Leads I and III of the initial record persisted and remained unaltered in subsequent records. This has been a constant and characteristic finding. Furthermore, the rela-

Fig. 11A.

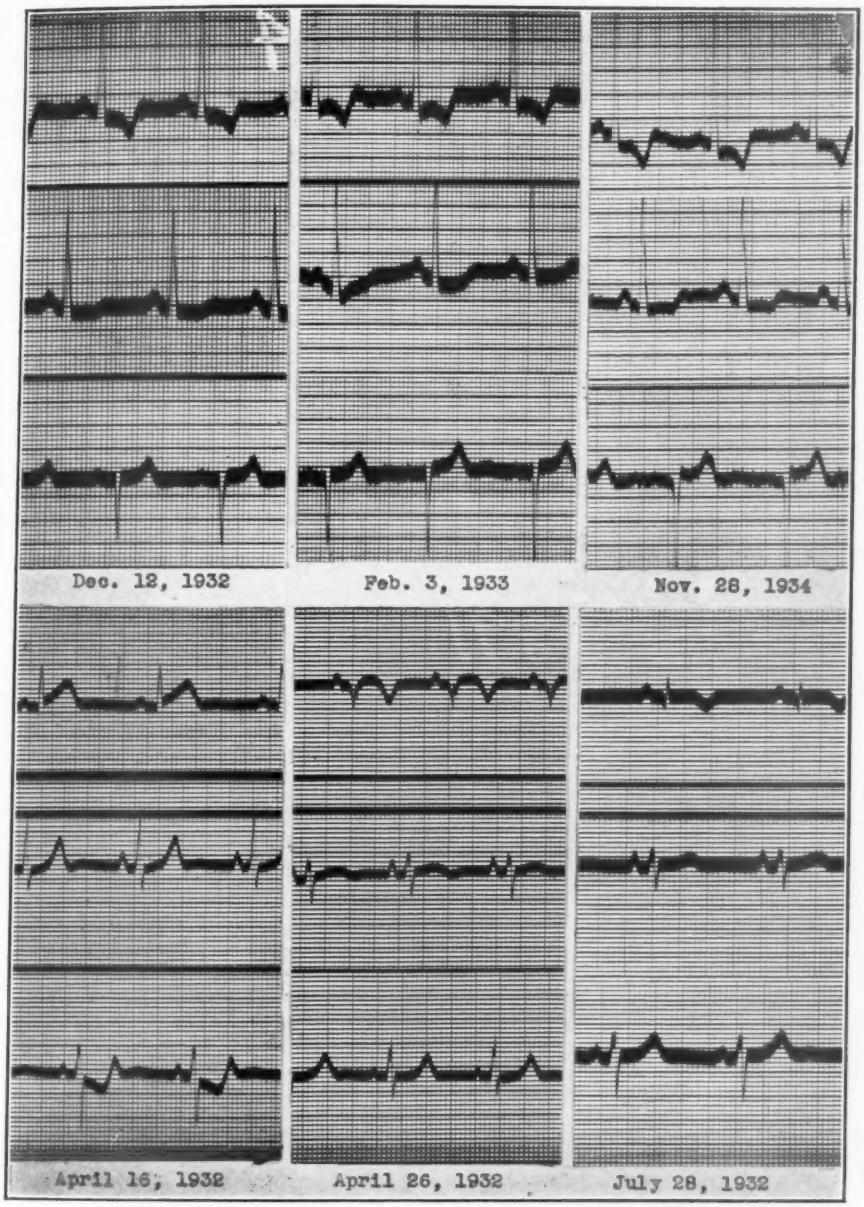

Fig. 11B.

tionship of the RS-T displacement to the T-wave deflection differs in these two series of electrocardiograms. In coronary thrombosis the RS-T deviation in Leads I and III occurs in a direction opposite to the T-wave deflection which develops later. Thus, in the T_1 type of record

the early upward displacement of the RT interval in Lead I is followed by an inversion of the T-wave in that lead. The reverse of this relationship of the RS-T segment to the T-wave is found in the records under discussion. The direction of the displacement of the RS-T segment in Leads I and III (Figs. 1 to 10 and Fig. 11A) conforms to the direction of the T-wave deflection so that in Lead I the RS-T segment takes off below the isoelectric potential and T_1 is a negative deflection, while in Lead III the RS-T interval is elevated above the isoelectric potential and T_3 is a positive deflection.

Another distinguishing feature of the electrocardiograms of this group of hypertensive patients is to be found in the T-wave deflection. In coronary thrombosis during the two to three weeks following the onset of the typical symptoms, the T-wave in Lead I or Lead III, depending upon the type, rapidly changes in form and amplitude. This T-wave change after a variable time may become stationary and persist indefinitely, or it may regress and eventually the electrocardiograms may return to normal. No such change in the form of the T-waves has been observed in the type of record under discussion. From a preliminary study, it would appear that when once established the T-wave and the RS-T defects described persist and remain unaltered until the death of the patient.

In part, the above combination of electrocardiographic defects has been described by Luten and Grove[2] in relation to hypertension. These observers, selecting electrocardiograms showing left axis deviation, T_1 negative, T_3 positive, and QRS of normal width, found that "in 70 per cent of 237 cases a reading at least as high as 170 mm. Hg had been recorded." Also, in a somewhat similar study Master[3] recorded the frequency of T-wave negativity, left axis deviation, and high voltage in electrocardiograms obtained from hypertensive patients. In neither of these reports, however, were alterations of the RT segment commented upon although in Fig. 2 of Luten and Grove electrocardiograms 1 and 3 show the significant changes in the RT segment here described.

CASES STUDIED

The present study was undertaken in order to determine the clinical interpretation of the unusual modification of the ventricular complexes referred to above. All electrocardiographic records taken at the Toronto General Hospital from 1921 to the end of 1932 were reviewed, and 152 out of a total of approximately 7,000 patients suffering from all forms of heart disease were found to have shown electrocardiographic changes conforming with the type described. The clinical histories of these patients, together with available autopsy data, were then reviewed. Those patients who had been discharged from hospital were followed through the out-

patient clinic, and patients known to be alive were brought back to hospital for further examination. In nine of the 152 cases many details of the history and physical examination were lacking. Therefore these cases were excluded and this report is based upon a study of the remaining 143 cases.

SYMPTOMS

It was found that cardiac symptoms predominated in this group of cases. Detailed histories were obtained in 126 of the 143 cases. In 95 the chief complaints were referable to the heart, and in only 5 of the 126 cases was a history of cardiac symptoms not obtained. Dyspnea on exertion, usually of long duration and of increasing severity, was the outstanding symptom and was present in 118 of the 126 cases. Less frequent was dyspnea of a nocturnal or paroxysmal type, which was observed in but 19 cases. Edema of the legs was reported in 60 cases. In 16 cases a history of a prolonged attack of substernal, precordial, or epigastric pain justified a diagnosis of coronary thrombosis, and in 2 of the 16 cases this diagnosis was proved to be correct by a post-mortem examination. Typical attacks of angina pectoris occurred in 28 patients. Cerebral symptoms, such as vertigo, irritability, loss of memory and insomnia, were common, being present in 74 of the 126 cases. Cerebral accidents, either hemorrhage or thrombosis, occurred in 20 cases. Urinary symptoms were rarely complained of although a history of nycturia was obtained in 62 cases.

AGE AND SEX

The average age of all patients was 55.8 years, 86 being males and 57 females. In Table I the cases are divided into age groups according to the presence or absence of hypertension. From Table I it will be noted that this electrocardiographic abnormality was of rare occurrence in patients under the age of forty years and was most frequently present in patients who had reached the sixth and seventh decades of life. Of

TABLE I

AGE OF PATIENT IN YEARS	NUMBER OF PATIENTS WITH H.B.P.		NUMBER OF PATIENTS WITH NORMAL B.P.
20-29	2		3
30-39	4		3
40-49	16		2
50-59	50		4
60-69	38		2
70-79	14		5
Total number of cases	124	+	19 = 143

6 patients under forty years of age who had hypertension, 4 had chronic nephritis, and 2 had malignant hypertension. None of the 6 had endocardial disease. These are to be compared with the 6 patients under

forty years of age who did not have hypertension. All 6 had aortic insufficiency, which was associated in 4 cases with aortic stenosis and in 2 cases with mitral stenosis.

CLINICAL FINDINGS

The remarkably high incidence of arterial hypertension among these patients was the important finding of the present study. Of 143 patients in the series, 124 (86.7 per cent) had arterial hypertension at the time the electrocardiographic records were obtained. In Table II the systolic and diastolic blood pressures of the hypertensive cases are recorded. These observations, in the majority of cases, were made while the patients were at rest in bed in the hospital. For the purposes of this study the patient who had a systolic blood pressure of 160 mm. Hg, or higher, was considered to have arterial hypertension. As will be seen from Table II, 83 (58.0 per cent of the whole series) had a systolic pressure of 200 mm. Hg, or over, and in 41 cases (28.7 per cent) the systolic pressure varied between 160 and 200 mm. Hg. The diastolic pressure readings were correspondingly high. In 67 cases (46.8 per cent) the diastolic pressure was found to be above 120 mm. Hg; in 40 cases (27.9 per cent) it was between 100 and 120 mm. Hg; and in only 17 cases was the diastolic pressure recorded below 100 mm. Hg.

In 19 of the 143 cases (13.3 per cent) the systolic pressure was found to be below 160 mm. Hg. In 7 of these 19 cases a systolic blood pressure of 150 mm. Hg was recorded on at least one occasion. In the remainder the systolic blood pressure varied between 100 and 142 mm. Hg. One patient who had aortic stenosis had on one examination a blood pressure of 130/110. Other readings on the same patient were 120/80 and 100/80, respectively. Three of these 19 patients had a diastolic pressure of 90 mm. Hg, and in the remainder the diastolic pressures were below this figure.

TABLE II

SYSTOLIC BLOOD PRESSURE MM. HG	NUMBER OF CASES	DIASTOLIC BLOOD PRESSURE MM. HG	NUMBER OF CASES
250-300	19	Over 160	5
225-249	17	140-159	22
200-224	47	120-139	40
180-199	31	100-119	40
160-179	10	Less than 100	17
Number of cases			124
Number of cases with normal blood pressure			19
Total number of cases			143

In all patients a diagnosis of myocardial disease was made. As was to be expected from the advanced age of the group as a whole, the incidence of degenerative heart disease was naturally high. Of the 143

patients studied in the series, 126 (88 per cent) had chronic degenerative heart disease. Eight patients had degenerative myocardial disease which was considered to be secondary to syphilitic aortic disease. Chronic rheumatic myocarditis was present in 11 cases and was complicated in 2 by subacute bacterial endocarditis. Seven of the 11 cases of rheumatic heart disease did not have hypertension. The size of the heart was determined accurately in 83 cases by means of orthodiagrams and in the remainder was determined by percussion. When only the 83 cases in which orthodiagrams were made are considered, moderate to marked cardiac enlargement was present in 73, and enlargement of slight degree was present in the other 10.*

Objective evidence of cardiac insufficiency, i.e., râles at the lung base, enlargement of the liver, and dependent edema, was found in 82 cases and was more often of moderate than of marked degree. It was probably related to paroxysmal or established auricular fibrillation in 18 of the 82 cases. In the remainder, congestive failure occured with a normal heart rhythm. A diagnosis of endocardial disease was made in 29 of the 143 patients. It was found in 11 of the 19 patients (57.8 per cent) whose systolic blood pressure was below 160 mm. Hg and in only 18 of 124 patients (14.5 per cent) with hypertension. It is noteworthy that aortic valve disease, either alone or combined with mitral lesions, occurred in 27 of the 29 patients who were found to have endocardial disease. Aortic insufficiency alone occurred in 11 patients; pure aortic stenosis in 6; combined aortic stenosis and insufficiency in 5, and aortic disease, either stenosis or insufficiency, was combined with mitral stenosis in 5. The remaining 2 of the 29 patients, both of whom had hypertension, had mitral stenosis.

Seventeen of the 19 nonhypertensive cases had congestive failure, and 11 of the 19 had aortic valvular disease. Of the remaining 8 nonhypertensive cases in which valvular lesions were absent, 3 had angina pectoris and 2 had angina pectoris and coronary thrombosis. Post-mortem examination was done in 1 of these 8 cases and revealed marked left ventricular hypertrophy unexplained by endocardial or pericardial disease. Further, orthodiagrams made on 4 of the remaining 7 cases all showed marked enlargement of the left ventricle. It is, therefore, probable that in these cases, as in the case that came to post-mortem, there had been preexisting hypertension.

POST-MORTEM FINDINGS

A complete post-mortem examination was made in 20 of the 143 cases. The average weight of the heart in 16 cases of hypertension was 587 gm. In 14 of the 16 hypertension cases the heart weighed over 450 gm., and in the remaining 2 the heart weighed 380 and 390 gm., respectively.

*These figures are based upon the assumption that the upper normal limit of the cardiothoracic ratio is 57 per cent[4].

The first of these 2 cases was a female, aged forty years, who had a basophilic adenoma of the pituitary gland, and the second was a male, aged forty-six years, who had chronic nephritis and uremia. In both cases a marked elevation of systolic and diastolic pressures had been repeatedly recorded. In 4 of the 20 cases examined post mortem the blood pressures had been found to be within normal limits while the patients were under observation. The weight of the heart in these four cases was 600, 885, 995, and 640 gm., respectively. The first 2 of these 4 patients had aortic stenosis of sclerotic origin. The third had rheumatic heart disease, aortic stenosis, aortic insufficiency, mitral stenosis, and chronic adhesive pericarditis. In the fourth case no endocardial or pericardial lesion was present which could account for the marked increase in the weight of the heart. In this, as in the other 3 cases, the left ventricle was hypertrophied. Preexistent hypertension was, therefore, likely in this case.

In the 2 cases of hypertension in which the heart weighed less than 400 gm., the left ventricle was moderately hypertrophied and measured 2 cm. in thickness. In the other 18 cases, hypertrophy of the left ventricle was marked, and the increase in the weight of the heart was due to a disproportionate increase in the weight of the left ventricle.

In 2 cases the coronary arteries were normal. In 8 cases the pathological changes in the coronary arteries were restricted to a few macroscopic atheromatous intimal streaks, the lumina of the vessels being widely patent. Five cases showed moderate arteriosclerosis and atheroma, and in 3 these changes were of advanced degree, accompanied by stenosis and calcification of the vessels. Actual occlusion of the artery by thrombus occurred in 2 of the latter cases. In 1 case old organized thrombi were found in the left circumflex and in the right descending coronary arteries; and in the other, a fresh dark red thrombus occluded the right coronary artery at a point of stenosis. In the first instance coronary thrombosis occurred before, and in the second case after, the significant electrocardiograms were taken. The myocardial lesions were variable and were lacking in any semblance of uniformity, and it was noteworthy that in 4 cases there were no demonstrable myocardial changes aside from hypertrophy of individual muscle fibers.

FOLLOW-UP STUDY

A follow-up study of these cases was made in order to determine the possible prognostic significance of these electrocardiographic changes. This study, as has been stated, covers a period of approximately twelve years and includes many recent cases. The duration of life has in all cases been estimated from the date upon which initial electrocardio-

graphic records of the type described were obtained. The cases with normal blood pressure and with hypertension have been dealt with separately.

First, of the 124 patients with hypertension, 20 could not be traced. Of the remaining 104 patients, 61 had died. The duration of life from the time of the first observation in 54 averaged 8.1 months and in the remaining 7, all of whom were known to be dead, the duration of life could not be ascertained. Forty-three patients with hypertension are still living, and at the time of writing the average duration of life of these patients was 17.1 months. The apparent discrepancy in these two average figures for living and dead patients is due to the fact that included with the latter are 4 patients who are still alive three, five and a half, seven, and eight and a half years, respectively, after the electrocardiographic record was obtained. If these 4 patients are excluded, the average duration of life for the living is reduced to 11.6 months.

In the smaller group with normal blood pressure, somewhat similar results were obtained. Of the 19 cases, 7 could not be traced. Eight of the remainder are dead, the average duration of life being 6.6 months. Four are still living, average duration of life being 39.5 months and the maximum being nine and a half years. Thus, of 109 patients accurately traced, 62 are dead; this gives an average mortality of 56.8 per cent in 7.9 months. There is, therefore, no doubt as to the seriousness of the prognosis in patients showing this electrocardiographic abnormality.

SUMMARY

It has been shown that electrocardiograms which exhibit the multiple abnormalities described differ from electrocardiograms of the T_1 type of coronary thrombosis. However, 16 of the 143 patients whose cases were reviewed had coronary thrombosis. In all 16 cases electrocardiograms showed the type of abnormality here recorded, and in none was the changing electrocardiographic picture of myocardial infarction found. Since 14 of these 16 patients had hypertension, the possibility must be kept in mind that antecedent or existing hypertension was the factor responsible for these abnormalities rather than cardiac infarction.

It has been found that arterial hypertension was present in 124 of the 143 patients and that 11 of the remaining 19 patients had aortic valvular disease; from the evidence available preexistent hypertension was probable in at least 5 of the other 8 cases. Thus, in these cases there was present one or other of the two most important factors which determine hypertrophy of the left ventricle. In addition, it was found that left ventricular hypertrophy was present in all cases examined post mortem. It would seem justifiable, therefore, to conclude that these distinctive

electrocardiographic abnormalities were characteristic of certain cases of left ventricular hypertrophy and, since arterial hypertension was by far the most frequent determining cause of that hypertrophy, that these electrocardiographic changes were practically diagnostic of hypertension. Further investigation regarding the relationship of these electrocardiographic abnormalities to left ventricular hypertrophy and to hypertension is in progress and will be reported upon later.*

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*Just before this paper was submitted for publication, a single record of similar electrocardiographic abnormality obtained from a patient with essential hypertension was published by the late Joseph H. Bainton and Julius Burstein, "Illustrative Electrocardiography," New York, 1935, D. Appleton-Century Company.

MORTALITY RATES OF ORGANIC DISEASES OF THE HEART BY GEOGRAPHICAL AREAS IN THE UNITED STATES*

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THE usual practice has been to present crude death rates of organic diseases of the heart by states or other subdivisions of the country, or to present data on the age-specific death rates for a few states or cites. This study was undertaken to determine what differences in mortality, if any, have existed in various ages among a large group of states. It will be seen later that a fair sample from all sections of the United States has been included in the group of thirty-six states studied.

All the data on mortality in this report have been taken from the Mortality Statistics reports of the United States Bureau of Census. Estimates of population have been made from the 1920 and 1930 census reports of the Bureau. The study was limited to the years 1922 to 1929, inclusive, because previous to 1922 deaths after thirty years of age were tabulated differently by age groups. The data for 1930, although available before this study was completed, were not included because doing so would have made little difference in the means of the calculated rates. Only data for states included in the death registration area in 1922 were used. Instead of a presentation of a large number of tabulations for each year for the thirty-six states, the mean or average rate for two four-year periods was used (1922-1925 and 1926-1929). This tended to smooth out fluctuations which were bound to arise from year to year when dealing with small groups of populations, as was the case in certain of the less populated states.

In this study only organic diseases of the heart have been included. In the classification used by the Bureau of Census in the Mortality Statistics reports from 1922 to 1929, deaths from organic diseases are to be found under four headings: (87) pericarditis, (88) endocarditis and myocarditis (acute), (89) agina pectoris, and (90) other diseases of the heart. The total number of deaths for each age listed under the four headings have been used in making the calculations for each group.

The states whose rates are tabulated in Tables I and II have been arranged in groups according to their geographical location, following much the same order which has been used by the Bureau of Census and the United States Public Health Service in various reports. This

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was done in order that a comparison of mortality rates for a whole group of states in the same geographical area might be made with other groups rather than a comparison of single states.

It was impossible to find a suitable standard with which individual states or groups of states could be compared. If the rates were calculated for the entire registration area they were heavily weighted by the large populations and large numbers of deaths from the Northeastern states. If the mean or average of the rates was taken for the thirty-six states, the rates of the states with small populations or those with few deaths caused the result to be low and equally unsatisfactory. It appears that a comparison of one group of states with another is most satisfactory.

It will be noted in Table I that mortality rates per 100,000 population have been tabulated for age groups under thirty years, and in Table II for the groups over thirty years and the crude rate for all ages. In discussing the data contained in these tables the mortality in the younger ages will be considered, then that of the older age groups and the crude rate. By so doing one can consider more readily organic diseases of the heart due to rheumatic and other acute infections among the young, and the degenerative forms which are limited to the older ages. The part that syphilis, also an infectious disease, plays in the mortality of middle life cannot be separated from that of the degenerative forms of heart disease in the data for the white race. Its effects seem somewhat more apparent in the data for the negro.

Numerous surveys have established the fact that rheumatic infections have accounted for most of the cases of organic diseases of the heart in the younger ages (under thirty years). If this assumption is true for all parts of the United States, a study of the mortality in the younger age groups for each state then should give us some indication of the prevalence of rheumatic infections in different sections of the country.

In Table I it is evident that there are certain sections of the United States where mortality rates due to organic diseases of the heart are much higher than others in the younger age groups. Comparatively high rates have prevailed in the states bordering on the Atlantic Coast from Maryland to Massachusetts, in two North Central states and in the Mountain states. The mortality under thirty years of age in these states is consistently above that of other areas. With the exception of the Mountain states this is not surprising.

Although Arizona and New Mexico were not included in the tabulations because they were not in the death registration area until recently, the available data indicate that their mortality for the group under ten years has been slightly under the general average for the

other states in the Rocky Mountain region but equally high for the age groups from ten to twenty-nine years. Why the Mountain states should have a high mortality is not clear, but the consistently high rates of these states seem to be fairly good statistical evidence that this relatively high mortality is of some significance.

It has been shown by a number of observers that rheumatic infections are more common in the northeastern part of the country than

TABLE I

MORTALITY RATE PER 100,000 POPULATION FOR ORGANIC DISEASES OF THE HEART FOR AGE GROUPS UNDER 30 YEARS, 1922-1925 AND 1926-1929

	UNDER 5		5 – 9		10 – 19		20 – 29	
	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929
New England								
Maine	16.6	19.8	4.9	5.4	11.9	13.2	16.9	15.5
New Hampshire	23.3	11.9	14.6	12.4	13.1	16.7	18.6	15.6
Vermont	12.9	12.6	4.4	6.5	14.7	13.7	15.8	19.8
Massachusetts	20.7	13.5	18.7	14.1	28.9	26.4	29.7	29.3
Rhode Island	25.2	20.3	15.2	12.7	20.4	21.4	25.3	24.9
Connecticut	16.9	15.7	14.9	12.9	20.5	21.9	23.8	26.0
Middle Atlantic								
New York	23.3	17.8	22.2	19.2	35.3	33.8	33.8	34.1
New Jersey	26.2	21.1	22.4	22.0	35.1	30.8	32.3	34.1
Pennsylvania	24.3	23.1	17.9	17.6	29.0	25.1	31.9	34.7
East North Central								
Ohio	14.9	12.4	13.2	10.5	21.3	18.5	25.6	25.2
Indiana	19.2	15.8	12.1	11.4	19.2	17.2	24.7	22.4
Illinois	23.7	21.1	19.8	18.0	25.4	25.4	30.1	31.9
Michigan	22.9	19.4	17.2	14.8	22.1	20.7	25.6	30.8
Wisconsin	13.1	13.1	9.5	10.4	16.5	16.0	19.5	18.5
West North Central								
Minnesota	9.0	7.5	8.7	8.4	16.4	15.0	21.3	20.6
Missouri	10.6	11.1	10.7	10.1	17.3	15.5	23.2	23.8
Nebraska	10.9	13.8	10.6	10.1	16.9	15.4	17.7	16.1
Kansas	14.6	13.3	8.9	5.8	11.2	11.2	17.1	16.8
South Atlantic								
Delaware	24.1	19.5	17.4	19.8	27.1	18.8	24.3	31.1
Maryland*	17.8	13.7	14.9	13.4	22.9	20.0	23.3	24.5
Virginia*	11.3	10.1	7.3	6.4	11.8	10.9	14.1	15.6
North Carolina*	9.9	10.8	5.9	5.3	8.1	10.7	17.7	16.9
South Carolina*	12.5	13.1	5.1	4.5	9.0	7.2	17.5	20.1
Florida*	15.9	10.4	4.4	9.4	8.7	10.7	21.0	24.5
South Central								
Kentucky*	12.3	11.5	5.5	5.9	10.8	9.0	17.2	17.9
Tennessee*	10.0	8.0	4.4	5.5	8.7	9.6	11.9	15.1
Mississippi*	8.1	7.5	3.5	4.6	8.2	6.3	11.1	11.9
Louisiana*	13.3	7.9	3.5	6.3	6.5	6.9	14.8	15.5
Mountain								
Montana	16.8	12.5	16.4	9.0	19.9	22.0	24.5	26.8
Idaho	18.6	14.5	17.7	12.3	20.2	20.9	20.7	23.9
Wyoming	11.8	27.5	18.6	15.5	26.6	21.1	20.4	22.5
Colorado	16.1	21.1	20.0	21.5	29.7	29.7	27.5	27.3
Utah	14.4	18.8	23.5	22.6	43.4	38.5	39.3	36.8
Pacific Coast								
Washington	8.9	7.2	10.5	9.8	18.3	14.8	17.4	19.3
Oregon	15.6	16.9	9.9	8.8	21.3	18.9	20.7	22.9
California	15.7	11.7	12.1	8.0	20.9	17.3	25.1	25.1

*Rates for white race only.

in the Southern states. However, mere geographical location does not appear to be the only important factor in the higher mortality rates, according to the evidence brought out in the present study. In most instances the upper New England states (Maine, New Hampshire, and Vermont) have had a much lower mortality than the other three New England states. The population of the latter differs from the former in that a greater proportion is concentrated in urban centers, a condi-

TABLE II

MORTALITY RATE PER 100,000 POPULATION FOR ORGANIC DISEASES OF THE HEART, OVER 45 YEARS AND FOR ALL AGES, 1922-1925 AND 1926-1929

	30 – 44		45 – 64		OVER 65		ALL AGES	
	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929
New England								
Maine	45.5	43.3	257	287	1954	2200	229	263
New Hampshire	49.9	51.6	292	357	1921	2228	241	291
Vermont	47.4	48.2	300	316	2173	2320	262	277
Massachusetts	68.9	71.5	369	398	2414	2539	235	269
Rhode Island	59.9	66.0	364	397	2140	2533	204	242
Connecticut	59.3	65.1	346	396	2185	2505	199	239
Middle Atlantic								
New York	80.1	83.8	436	485	2598	2931	246	277
New Jersey	80.8	85.7	383	447	2251	2558	206	240
Pennsylvania	73.3	82.5	346	411	2041	2454	187	229
East North Central								
Ohio	56.8	69.1	270	326	1836	2125	177	216
Indiana	41.9	59.5	259	308	1760	2073	187	225
Illinois	71.0	82.7	320	387	1999	2328	186	227
Michigan	61.9	80.0	293	344	2032	2335	183	211
Wisconsin	42.9	49.5	237	267	1736	2056	159	194
West North Central								
Minnesota	46.9	47.8	235	250	1738	1837	144	171
Missouri	54.4	64.9	229	286	1377	1738	145	192
Nebraska	38.1	41.9	210	237	1338	1275	122	158
Kansas	39.1	40.7	189	219	1463	1712	139	168
South Atlantic								
Delaware	65.6	85.1	328	383	1897	2075	201	242
Maryland*	58.3	64.2	316	364	2039	2309	194	229
Virginia*	41.5	41.7	245	271	1832	2146	138	164
North Carolina*	39.2	46.1	212	251	1562	1956	109	128
South Carolina*	47.3	53.5	254	287	1765	2205	112	138
Florida*	50.5	60.7	275	319	1511	1768	149	179
South Central								
Kentucky*	37.2	43.5	177	244	1276	1500	106	129
Tennessee*	31.8	37.5	155	193	1159	1456	88	110
Mississippi*	26.4	34.7	171	200	1264	1568	91	110
Louisiana*	64.2	40.7	295	325	1922	2193	127	147
Mountain								
Montana	44.7	59.6	225	272	1459	1757	105	152
Idaho	39.5	47.7	179	238	1257	1586	92	134
Wyoming	47.7	29.9	221	211	1270	1483	95	110
Colorado	55.0	56.4	225	259	1363	1662	131	166
Utah	72.2	67.4	246	281	1473	1797	123	148
Pacific Coast								
Washington	40.5	45.8	245	268	1561	1912	145	185
Oregon	46.3	48.8	256	279	1651	2003	170	212
California	61.0	60.3	327	342	2109	2273	234	240

*Rates for white race only.

tion which is said to predispose to a greater incidence of rheumatic infections. The question whether a large proportion of foreign-born in a population predisposes to a greater prevalence of rheumatic infections might be raised, but there is no definite evidence on this point to be found in the available data. The effect of crowding, types of housing, and other environment factors would necessarily have to be taken into consideration before claiming that a particular nationality is more or less susceptible to acute rheumatic fever and rheumatic heart disease. However, the fact remains that in Maine, New Hampshire, and Vermont in 1930 the ratio of native white to foreign-born white was approximately 8 to 1 while the ratio for the other New England states was 4 to 1.

In general, the populations of the Middle Atlantic states and Illinois and Michigan show about the same general conditions regarding percentage of urban population and foreign born as is found in the lower New England states. However, the Mountain states present a different picture. On the average only about 37 per cent of the population is classed as urban in contrast to 81 per cent in Massachusetts, Rhode Island, and Connecticut, 78 per cent in the Middle Atlantic states, 71 per cent in Illinois and Michigan, and 55 per cent in Delaware and Maryland. Even among the Mountain states themselves, those with the highest percentage of urban population, namely, Colorado and Utah, have the highest mortality from diseases of the heart. In the Mountain states the proportion of foreign born is much lower than in the East. Climate is another variable which is quite different in the two areas.

In 1930 Viko[1] stated that rheumatic heart disease accounted for a greater percentage of all organic diseases of the heart observed in a clinic whose patients lived in or near Salt Lake City than is the case in some other parts of the country, but he presented no evidence to indicate whether or not rheumatic heart disease is actually more prevalent in that section than elsewhere.

Data for the Southern states and west North Central states in the younger age groups indicate that mortality from organic diseases of the heart is much lower in these regions than in any other sections of the country, a fact which is consistent with the usual conception of rheumatic infections in these areas.

From the data presented it would not be unreasonable to assume that rheumatic diseases of the heart, and probably rheumatic fever also, are about as common in the Mountain as in the Eastern states. If not as common, they probably are more fatal. Studies on the epidemiology of acute rheumatic fever and rheumatic heart disease in the Rocky Mountain area would be of great value in answering these questions.

A slightly different picture is presented for the older age groups, particularly over forty-five years. In general, the states, except for the Mountain states with the higher mortalities in the younger age groups, are ranked in about the same order for the older age groups. In this instance, the mortality for the Mountain states is found to be below that of other areas.

In spite of the fact that the upper New England states have a greater proportion of their population over forty-five years old their death rates are lower than those for the lower New England states in these age groups. Certain southern states show relatively higher rates in the older age groups than in the younger age groups.

Fig. 1 illustrates graphically some of the points previously mentioned. The mortality rates of three geographical areas for each age group in the four-year period from 1926 to 1929 were charted on a semilogarithmic scale. The mean mortality rates for the period appear in the ordinates on a logarithmic scale, and the ages in the abscissae on a uniform scale of years. Such a method will indicate the relative or percentage difference in the rates from one age to another and the relative difference of various groups in the same age. Since the mortality rates show an enormous numerical range from the younger to the older ages, a semilogarithmic chart is more satisfactory because it shows the relative or percentage differences very readily without distortion.

In this chart the similarity of mortality rates in the younger age groups for the Middle Atlantic and the Mountain states is apparent. The Middle Atlantic states were chosen because it has been known that rheumatic fever and organic diseases of the heart have shown a high incidence and mortality in this area for a number of years. Fig. 1 also shows that the percentage difference in the older age groups as compared with the younger is greater for these eastern states than the Mountain states. It also shows the wide difference which exists in the groups under thirty years of age when the mortality of the Southern states is compared with the Northern. However, in the age groups over thirty years the difference in the two areas is less, and the mortality increases with age at approximately the same rate in the South Central area as in the Middle Atlantic.

When considering the crude death rates it is necessary only to point out that the high mortality rate for all ages of the upper New England states covers up the fact that their rates for each age group is generally lower than that of the lower New England states. The reason for this is merely that the population of the former contains a greater percentage of persons over the age of forty-five years, the age when most deaths occur. It is likewise evident that the low crude rate of

the Mountain states covers up the fact that a high mortality exists in the younger age groups. On the other hand, the crude rate of certain southern states masks a relatively higher mortality in the older age groups.

So far the mortality rates of organic diseases of the heart have been considered for the white race only. Crude rates whenever available have indicated that the mortality is greater among negroes than among whites. In the data presented in Table III for the white and colored rates in nine southern states, it is evident that the negro rates are higher in all ages except after 65 years.

The greatest difference in the mortality rates among the two races is to be found in the group from thirty to forty-four years of age, when

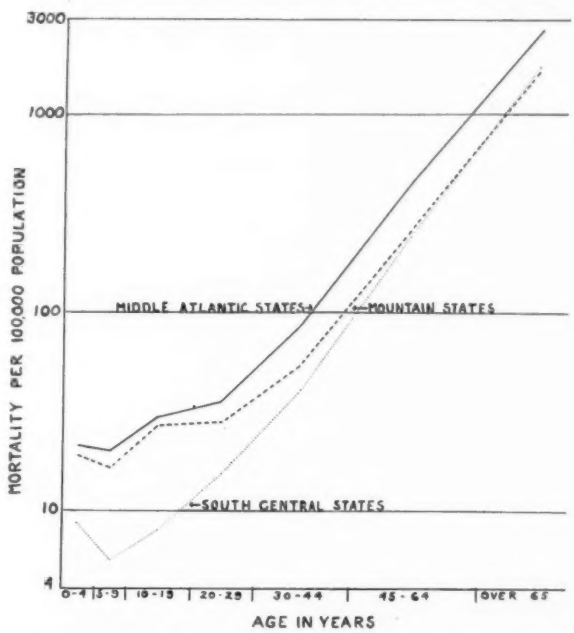

Fig. 1.—Mean mortality rates for organic diseases of the heart by age groups in the Middle Atlantic, Mountain, and South Central states, 1926-1929.

the negro rate is from three to five times that of the white. There is no definite evidence that the greater prevalence of syphilis among negroes accounts for this great difference, but the probabilities are that this is the case.

After sixty-five years of age the mortality of whites is often higher than among negroes. The fact that coronary diseases and certain other types of degenerative forms of heart disease are less frequently reported as the cause of death among negroes no doubt accounts for the fact that the mortality for organic diseases of the heart among negroes is often less than for the white race after the age of sixty-five years.

TABLE III

MORTALITY RATE PER 100,000 POPULATION FOR ORGANIC DISEASES OF THE HEART IN THE WHITE AND NEGRO RACES OF THE SOUTHERN STATES, 1922-1925 AND 1926-1929.

	0-4		5-9		10-19		20-30		30-44		45-64		OVER 65		ALL AGES	
	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929	1922 TO 1925	1926 TO 1929
Florida																
White	15.9	10.4	4.4	9.4	8.7	10.7	21.0	24.5	50.5	60.7	275	319	1511	1768	149	179
Negro	9.0	10.4	9.2	10.3	16.1	18.6	52.5	62.3	168.7	208.4	441	565	1272	1377	146	179
Kentucky																
White	12.3	11.5	5.5	5.9	10.8	9.0	17.2	17.9	37.2	43.5	177	244	1276	1500	106	129
Negro	21.5	19.6	6.6	5.7	26.6	23.8	50.5	58.4	204.1	219.1	635	780	1577	2097	264	325
Louisiana																
White	13.3	7.9	3.5	6.3	6.5	6.9	14.8	15.5	64.2	40.7	295	325	1922	2193	127	147
Negro	10.5	10.8	7.6	10.6	15.4	17.2	53.3	62.3	192.2	219.6	593	714	2021	2444	198	233
Maryland																
White	17.8	13.7	4.9	13.4	22.9	20.0	23.3	24.5	58.3	64.2	316	364	2039	2309	194	229
Negro	33.9	18.0	19.6	12.2	26.0	14.9	48.1	55.5	195.4	228.0	719	800	1990	2191	251	273
Mississippi																
White	8.1	7.5	3.5	4 6	8.2	6.3	11.1	11.9	26.4	34.7	171	200	1264	1568	91	110
Negro	6.7	7.4	7.6	6.3	14.2	11.9	37.9	41.2	106.6	115.0	326	371	1296	1341	118	127
North Carolina																
White	9.9	10.8	5.9	5.3	8.1	10.7	17.7	16.9	39.2	46.1	212	251	1562	1956	109	128
Negro	11.8	10.2	9.9	7.2	16.7	20.6	50.4	56.7	142.9	176.2	444	548	1643	1929	142	165
South Carolina																
White	12.5	13.1	5.1	4 5	9.0	7.2	17.5	20.0	47.3	53.5	254	297	1265	2205	112	138
Negro	10.5	16.2	6.9	7.5	13.6	17.4	71.0	90.4	187.2	256.0	478	674	1620	1786	138	191
Tennessee																
White	10.0	8.0	4.4	5.5	8.7	9.6	11.9	15.1	31.8	37.5	155	193	1159	1456	88	110
Negro	11.6	5.6	6.8	10.3	14.0	18.0	50.5	56.4	165.2	187.4	482	618	1383	1700	177	215
Virginia																
White	11.3	10.1	7.3	6.4	11.8	10.9	14.1	15.6	41.5	41.7	245	271	1832	2146	138	164
Negro	10.6	12.9	8.0	7.2	18.5	18.6	56.4	54.4	211.2	236.0	633	810	1709	2037	203	256

Fig. 2 is a graphic representation of the difference in the white and colored races for the South Central states. All of the Southern states show very much the same picture, i.e., little difference in mortality at the extremes of life and a marked difference in the middle ages.

Although the period of time covered in this study is comparatively short, the mortality has shown some decrease in the younger age groups in certain parts of the country, particularly in the northeastern section. This reduction may be due partly to a decline in the incidence of acute infectious diseases other than rheumatic fever. This is an encouraging sign, even though we have no specific prophylactic meas-

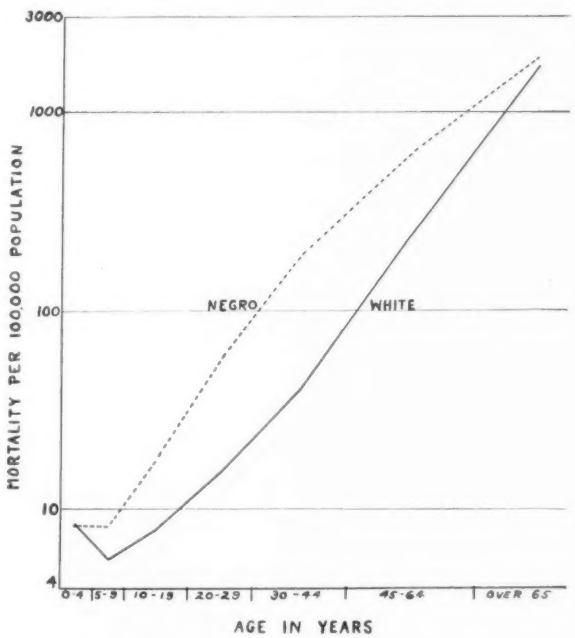

Fig. 2.—Mean mortality rates for organic diseases of the heart by age groups for the white race and negroes in South Central states, 1926-1929.

ures for organic heart disease. In the group over forty-five years, however, a very evident increase in mortality has occurred. More adequate treatment of syphilis in the negro is suggested as one means of preventing many deaths from heart disease in the middle ages of that race.

SUMMARY

Mortality rates for organic diseases of the heart in the younger age groups are high in the Atlantic Coast states from Maryland to Massachusetts, in Illinois and Michigan, and in the Mountain states. The areas with low rates are the west North Central states, and most of the Southern states.

In the older age groups the Northeastern states show the highest mortality. The Mountain area has a relatively low death rate and the Southern states, a higher rate in contrast to the mortality in the younger age groups.

The negro mortality rates in the Southern states for organic diseases of the heart are generally higher than for the white race. The greatest difference is found in the group from thirty to forty-four years of age. It is probably due to a greater incidence of syphilis among negroes.

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A MODIFICATION OF THE WIGGERS-DEAN METHOD OF RECORDING HEART SOUNDS USING AUDIO AMPLIFICATION*

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THE object of this paper is to describe a practical inexpensive method of recording heart sounds that may be used clinically to show the intensity of murmurs and their location in the cardiac cycle.

Many amplifiers for recording heart sounds have been described in the past. A brief review of the history of sound recording has recently been presented by Bierring and his coworkers[1] who also describe a new type of apparatus for recording heart sounds which requires the use of a galvanometer.

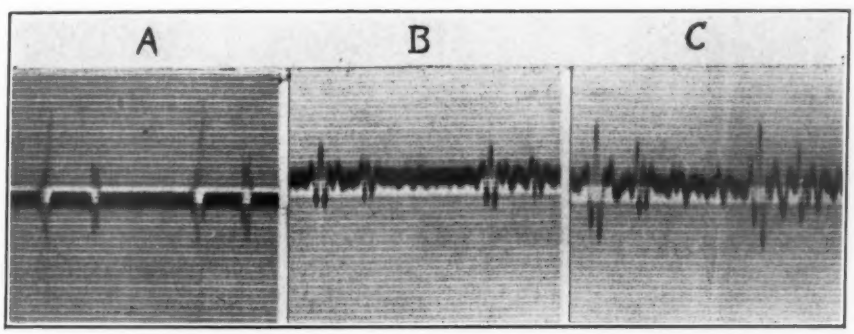

Fig. 1.—Normal heart sounds, recorded from apex: *A*, with crystal microphone method; *B*, with direct Wiggers-Dean method damped; *C*, with direct Wiggers-Dean method undamped.

The method which we have used, utilizes a crystal microphone, the advantages of which have been described elsewhere by Sacks and Marquis.[2] A three-stage audio amplifier, which measures 7.5 inches in height, 8 inches in width, and 9 inches in length complete with batteries, was designed and built by one of us (H. M.) for use with the microphone. For recording, an output receiver from the amplifier is connected with a Wiggers-Dean heart sound segment capsule.[3] This method differs from the direct Wiggers-Dean method in that amplified filtered sounds excite the membrane of the segment capsule instead of unamplified sounds picked up directly from the chest. No damping is used with the microphone method as damping introduces extraneous oscillations in the base line.

*From the Heart Station, Michael Reese Hospital, Chicago.

The time values of the heart cycle are set either by recording Lead II of the electrocardiogram simultaneously with the heart sounds or by using the optically recorded carotid or subclavian arterial pulse tracing (Wiggers[4]). The camera is speeded up in order to spread out the sound tracing and make the interpretation easier.

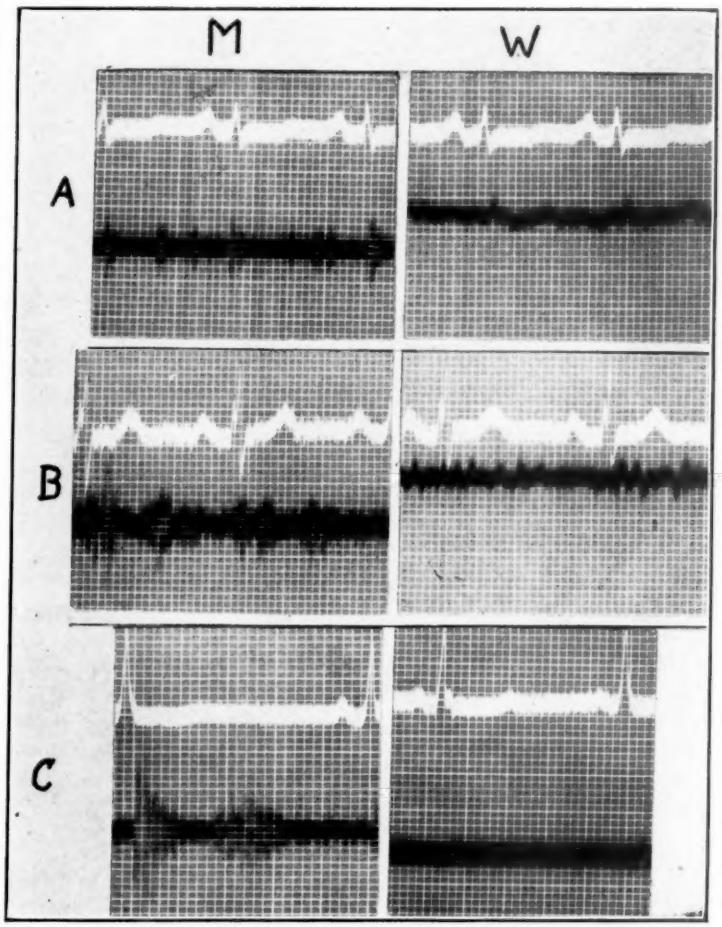

Fig. 2.—Records *M*—heart sounds taken with microphone amplifier method; records *W*—with direct Wiggers-Dean method on the same patient; in both the heart sounds were recorded simultaneously with Lead II. *A*, record of sounds from aortic area, showing diastolic murmur. Clinical diagnosis was rheumatic heart disease, aortic insufficiency. *B*, record of sounds from aortic area, showing systolic and diastolic murmurs, in case of syphilitic heart disease, with an aortic aneurysm. *C*, record of sounds from aortic area records, showing definite diastolic murmur in a case of syphilitic heart disease with clinical findings of aortic valve insufficiency.

The direct Wiggers-Dean method of recording heart sounds usually gives good results with careful technic in appropriate subjects. But when the sounds are distant as in emphysema and obesity[3] and in dyspneic patients, satisfactory tracings have been difficult to obtain. It

is also difficult to record sounds from the base of the heart, and certain murmurs may be missed. Margolies and Wolferth[5] have called attention to the limitations of the direct Wiggers-Dean method in the recording of high-pitched sounds and have utilized an audio amplifying system with the Wiggers-Dean capsule method to overcome this difficulty. These difficulties in recording are also overcome to a large extent with the amplifier system we employed.

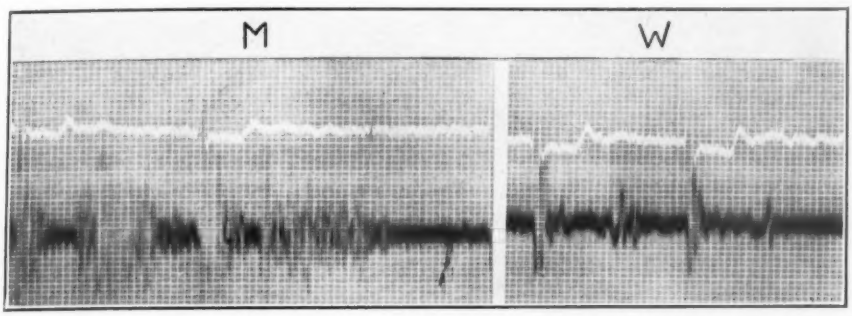

Fig. 3.—Records of heart sounds together with Lead II of electrocardiogram obtained from apex in a case of rheumatic heart disease and auricular fibrillation, showing systolic and diastolic murmurs. Record *M*, taken with microphone amplifier method. Record *W*, taken with direct Wiggers-Dean method.

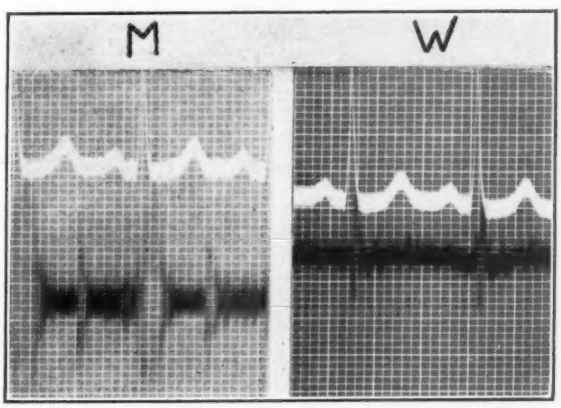

Fig. 4.—Records of heart sound together with Lead II of electrocardiogram obtained from apex in a case of rheumatic heart disease, showing systolic and diastolic murmurs. Record *M*, taken with microphone amplifier method. Record *W*, taken with direct Wiggers-Dean method.

Clinical use of the crystal microphone amplifier apparatus has produced satisfactory records from the apex and base of the heart (Figs. 1, 2, 3, and 4). In all patients tested, distant heart sounds and murmurs, including the soft diastolic aortic murmurs, were recorded satisfactorily, even when the direct method was inadequate. All tracings were free from extraneous vibrations, and the localization in the cycle of normal and abnormal cardiac sounds presented no difficulties.

A "tone control" has been introduced into the circuit, which was found to be valuable in estimating roughly the vibration frequency range of the murmurs.

SUMMARY

A method of recording heart sounds, which uses the crystal microphone with an audio amplifier system, together with the Wiggers-Dean sound segment capsule is described. This method was found satisfactory for clinical use and was found to avoid many of the difficulties present in the direct Wiggers-Dean technic.

The authors wish to acknowledge their indebtedness to Dr. L. N. Katz for his valuable advice and criticisms in developing this method.

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Department of Clinical Reports

AN EXTRAORDINARY DEGREE OF PARTIAL HEART-BLOCK

Report of a Case in Which the P-R Interval Exceeded the R-R Interval*

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DELAY in auriculoventricular conduction is a relatively common sign of myocardial involvement, whether caused by inflammatory changes in the conducting tissues as in rheumatic fever or by nutritional disturbances as in coronary sclerosis. High grades of A-V block, i.e., P-R intervals of more than 0.40 sec., are seldom encountered, however, on account of two limiting factors. In the first place, with the higher grades of heart-block the refractory period of the A-V node tends to be so prolonged that impulses become completely blocked there, producing "dropped beats" or a regular two to one or even lower ratio of ventricular response. The second limiting factor is the inherent rhythmicity of the ventricular pacemaker which causes it to "escape" if the impulse from the supraventricular pacemaker is delayed too long. The case here recorded is remarkable in that the ventricle remained dependent on the sino-auricular pacemaker in spite of the fact that the A-V conduction interval was on occasions so long that a second auricular systole had taken place before the impulse from the first auricular systole had reached the ventricle.

The patient (Hosp. No. 645597) was an unemployed laborer who was first admitted to the Second Medical Service of the Boston City Hospital on Aug. 1, 1931, complaining of precordial pain, dyspnea, and episodes of amnesia. He was fifty-six years old at the time.

His family history revealed that his father had died at seventy of apoplexy, and his mother had died at sixty-seven from an unknown cause. His wife had died of "tuberculosis of the stomach" many years before, leaving two healthy children.

At the age of eight years he had had diphtheria, requiring tracheotomy. He had had gonorrhea in his youth and a typical attack of rheumatic fever at thirty-three years. At thirty-seven he passed an examination for life insurance. On account of repeated sore throats, a tonsillectomy was performed at the age of forty-nine years. He had served three enlistments in the Navy following the Spanish-American War and worked at various odd jobs thereafter.

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

Early in 1926 he began to suffer from shortness of breath, swelling of the ankles, and "skipping of the heart." On Mar. 15, 1926, during a period of marked "skipping of the heart," he suddenly lost the power of speech and then became unconscious. He was brought to the Chelsea Naval Hospital where he gradually emerged from his coma over a period of several days. A residual right facial weakness and aphasia slowly cleared up during his seven months' stay in that hospital. On admission to the Naval Hospital it was noted that the heart rhythm was regular except for occasional dropped beats and that the heart sounds varied in intensity. Pulsus alternans was present to a striking degree, the systolic blood pressure alternating between 112 and 130 mm. Hg and the diastolic between 60 and 70 mm. Hg. There were no signs of congestive failure. The urine showed a slight trace of albumin, and the nonprotein nitrogen in the blood was 56 mg. per 100 c.c. Before his discharge from the hospital the systolic blood pressure had risen to a level of 170-180 mm. Hg and the diastolic to 96-104 mm. Hg, the alternation persisting. The nonprotein nitrogen in the blood fell to 33 mg. per 100 c.c.

His next hospital admission was to the Third Medical Service of the Boston City Hospital on Mar. 8, 1927, on account of a pulmonary embolism from which he made an uneventful recovery. The pulse rate at this time was slow, varying between 40 and 60 beats per minute.

During the year 1931 he suffered from increasing dyspnea and precordial pain and had three amnesic episodes preceded by severe headache and vertigo, lasting for seven or eight hours. These episodes were followed by temporary aphasia. His memory for recent events became poor. He was admitted to the Second Medical Service of the Boston City Hospital on Aug. 1, 1931. Physical examination at that time showed an obese, florid man with a slight residual facial paralysis on the right. There was moderate peripheral arteriosclerosis. The heart sounds were distant, slow and regular except for occasional brief accelerations. There was a systolic murmur at the apex. The chest was emphysematous. There were varicose veins with eczema but no edema of both lower legs. The tendon reflexes were all hypoactive. During his stay of five weeks in the hospital, the pulse rate varied between 45 and 70 beats per minute and the blood pressure between 140 and 160 mm. Hg systolic and 85 to 100 mm. Hg diastolic. The blood Kahn reaction, the urine, and the blood cytology were all normal.

He was discharged from the hospital improved but remained a cardiac invalid with angina decubitus. In January, 1933, he developed a particularly severe attack of precordial pain radiating down both arms and lasting for eighteen hours, unrelieved by nitroglycerine. On readmission to the hospital a week later he was orthopneic and showed coarse râles at the base of the right lung. There was a leucocytosis of 11,000 per c.mm. which persisted for four weeks. He remained in the hospital for five months and was again discharged improved.

Four weeks later, however, he was brought to the hospital for the last time. The oral temperature was 97° F., the pulse rate, 100, and the respiratory rate, 30 per minute. There was some cyanosis of the lips. The heart appeared enlarged; the sounds were distant and regular. The lungs were clear. The blood pressure was 165 mm. Hg systolic and 85 mm. Hg diastolic. There was a persistent leucocytosis of from 14,700 to 20,500 per c.mm. of blood. The hemoglobin was 116 per cent. The nonprotein nitrogen in the blood was 42 mg. per 100 c.c. A teleroentgenogram of the heart showed marked enlargement of the heart and great vessels. He continued to suffer from frequent attacks of dyspnea, cyanosis, and substernal pain, and in one of these attacks he died on July 7, 1933. His treatment during his several hospital admissions consisted largely of rest and sedation, digitalis having been given only once for a brief period at the time of his first admission to the

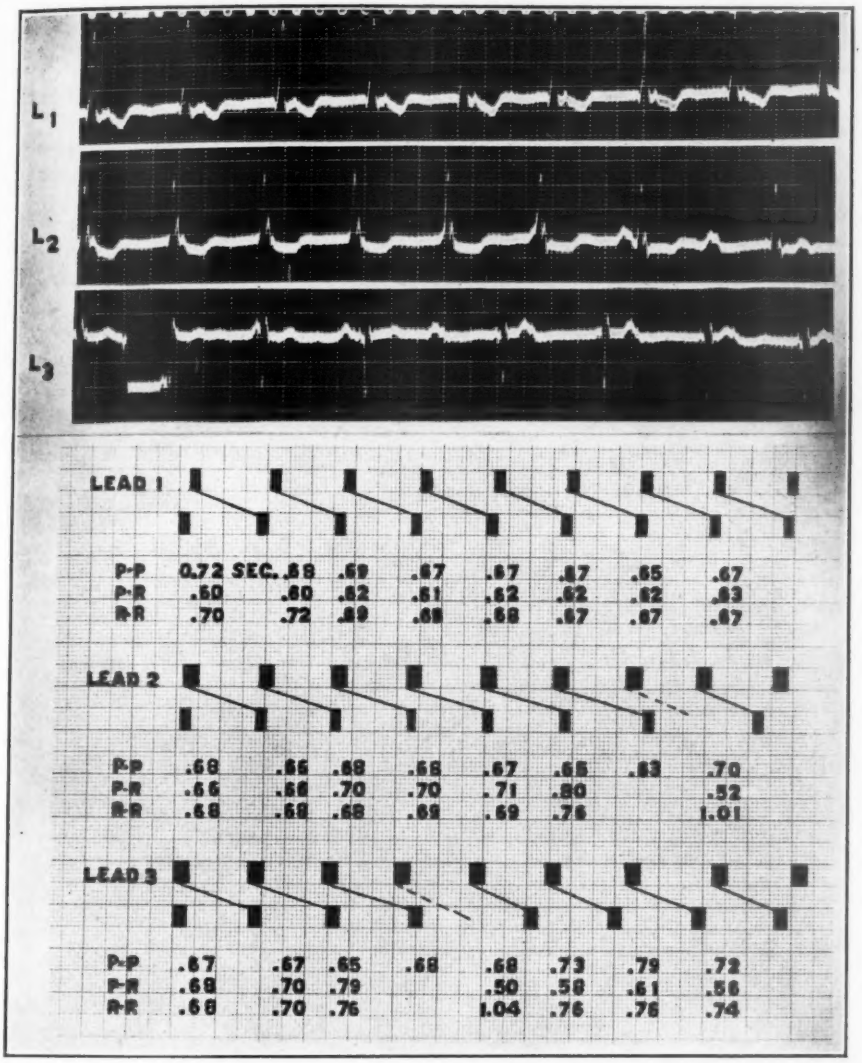

Fig. 1.—*Above*, electrocardiogram taken Jan. 18, 1933, patient B. S., aged fifty-eight years.

Below, diagrammatic representation of same record. The upper line of blocks in each series represents auricular contraction; the lower line represents ventricular contractions; and the connecting lines between them, the conduction intervals. The heavy lines on the background are spaced to indicate intervals of 0.20 sec. and the light lines to indicate 0.04 sec. In Lead I the P-waves are superimposed on initial part of the T-wave and latter part of the R-waves. In Lead II the P-waves are buried further back in the R-waves at the beginning of the record and may be seen to emerge before the preceding R-waves at the fifth and sixth ventricular complexes. The seventh auricular contraction results in a dropped beat. In Lead III the P-wave of the auricular contraction controlling the fourth ventricular contraction may be seen emerging before the third ventricular complex. The next auricular contraction results in a dropped beat. The P-R interval exceeds the R-R interval on five occasions on this record.

Boston City Hospital. The pertinent clinical diagnoses were: arteriosclerosis; coronary sclerosis; coronary thrombosis, old and recent; and partial heart-block.

A total of seventeen electrocardiograms were taken between 1926 and 1933. Through the kindness of Dr. David Ferguson, I was permitted to examine the records taken at the Chelsea Naval Hospital. Most of the records showed a high degree of partial heart-block with P-R intervals ranging from 0.36 sec. to 0.84 sec. As early as Apr. 1, 1926, a record showed P-R intervals of 0.72 sec. On two occasions, once in 1926 and again in 1931, complete heart-block was recorded. Other changes in the electrocardiogram developed during the period of observation. Notching and widening of the QRS complexes appeared and the axis shifted to the left. A deep Q-wave and inverted T-wave appeared in Lead III in 1931, only to disappear the following year as inverted T-waves began to appear in Leads I and II. No significant changes occurred in the electrocardiogram following the record illustrated in Fig. 1. In both Leads II and III of Fig. 1 examples of P-R intervals exceeding R-R intervals may be seen. A diagrammatic sketch of the sequence of events in the electrocardiogram is shown below the tracing.

Autopsy was performed twenty-six hours post mortem by Dr. John Hayes. The significant findings were as follows: There was pitting edema of the legs up to the hips, but the lower edge of the liver was at the costal margin, and there was no free fluid in the serous cavities.

The heart was enlarged, weighing 740 gm. The left ventricular cavity was markedly dilated and contained, attached to the intraventricular septum, a partially organized thrombus measuring 4 by 2.5 cm. The right ventricle was also dilated. The myocardium was reddish brown in color, firm, and showed no gross evidence of fibrosis. The thickness of the left ventricle was 1.4 cm., and of the right ventricle 0.6 cm. There was marked atheromatous degeneration of the coronary arteries, aorta, and aortic cusps.

The lungs showed multiple areas of infarction. The liver weighed 1,900 gm. and the lobules of the liver stood out prominently from its cut surface.

The kidneys were small and finely granular, and the right kidney contained an old infarct.

The anatomical diagnoses (from the gross examination) were: hypertensive heart disease, pulmonary infarction, mural thrombus, cardiac hypertrophy, infarct of the kidney, benign nephrosclerosis, marked chronic passive congestion of the liver, and marked atheromatous degeneration of the coronary arteries and aorta.

Microscopical examination of the heart showed marked deposit of cholesterin beneath the intima of the coronary arteries. The myocardium exhibited a moderate degree of fibrosis which became marked in the papillary muscle where relatively large areas of the muscle cells were destroyed. The small papillary muscle was surrounded by a partially organized thrombus and showed subendocardial fibrosis with early necrosis and a monocytic infiltration of the central portion. Four sections were taken from the intraventricular system. The bundle of His or its branches could not be positively identified in any of these. There was fibrosis in this region, and the muscle fibers showed a tendency to stain poorly or to take an acid stain, with pyknotic nuclei. Such changes were most marked just beneath the endocardium.

The liver showed marked distention of the central sinusoids with erythrocytes while the adjacent liver cells stained poorly with the acid stain and were being infiltrated by polymorphonuclear leucocytes and monocytes. The kidneys showed marked fibrous thickening of the intima of the small arteries with focal areas in which tubules and glomeruli stained more or less homogeneously with acid stain, showing little structural differentiation. Adjacent glomeruli were fibrosed or stained

poorly, with marked thickening of the interstitial fibrous tissue. The lumina of one of the larger and several of the smaller arteries were filled with loose fibrous tissue containing one or two small canaliculizing vessels.

The microscopical diagnoses were: marked atheromatous degeneration of the coronary arteries, moderate perivascular fibrosis of the myocardium, mural thrombus (left ventricle), pulmonary infarcts, hemorrhagic central necrosis of the liver, old infarct of the kidney, and advanced atheromatous degeneration of the aorta.

DISCUSSION

This case is comparable, with regard to the length of the P-R interval, to that reported in 1915 by the late Dr. W. S. Thayer.[1] Dr. Thayer's case was that of a woman fifty-five years old who suffered from extreme bradycardia with occasional syncopal and eclamptic attacks. The pulse rate averaged about 30 per minute. The P-R interval in the electrocardiogram was often more than 0.7 second, and on one occasion it reached 0.88 second. In polygraphic tracings the a-c interval amounted to 0.7 to 1 second. These appear to be the longest recorded A-V conduction times on record. The feature which makes the case here reported unique is that, in spite of an extraordinary delay in conduction, the sinus rate was usually normal or increased so that the P-R interval approximated, and on occasions actually exceeded, the R-R interval. It is noteworthy also that under these circumstances variation in intensity of the first sound of the heart was noted comparable to that observed in complete heart-block and attributable to the same cause, i.e., occasional synchronous contraction of auricle and ventricle.

SUMMARY

A case of extreme degree of partial heart-block is reported on which observations were made over a period of seven years. The P-R interval on one occasion reached 0.80 second, actually exceeding the R-R interval.

REFERENCE

1. Thayer, W. S.: Adams-Stokes Syndrome—Persistent Bradycardia, Involving Both Auricles and Ventricles. Remarkable Prolongation of the A_s-V_s Interval, Tr. A. Am. Physicians **30**: 63, 1915.

PATENT DUCTUS ARTERIOSUS COMPLICATED BY ENDOCARDITIS AND HEMORRHAGIC NEPHRITIS*

A Case Report

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PULMONARY endarteritis and endocarditis are well known as complications of patent ductus arteriosus. Several adequate reviews are in existence.[1] Since Blumer and McAlenney's discussion, which included twenty-two cases from the literature and six original cases, five additional instances have been reported.[2] These, together with the case here set forth, bring the total of reported cases to 34.

The present case was thought worthy of record because it was closely followed through its entire course; an acute hemorrhagic nephritis developed under observation; and detailed post-mortem studies were possible.

CASE REPORT

M. D., an American schoolgirl, aged eighteen years, was admitted to the medical service of Lane Hospital on July 13, 1931, complaining of fever and weakness for three weeks.

In early childhood a congenital heart lesion had been discovered, and she had never been allowed strenuous exertion. Her health had been excellent, however, and she said she was a "good walker." There was no history of rheumatic infection. Tonsillectomy had been performed at the age of seven years.

About three weeks before entry she began to feel bad on awakening in the morning, to have vague abdominal pains, and to notice weakness and anorexia. She was found to have afternoon fever, sometimes as high as 39.5° C. Because the fever and symptoms persisted, she entered the hospital.

Examination revealed a pale, thin girl, who did not look ill. The temperature was 38.3° C. (rectal); the pulse, 116; respirations, 20; blood pressure, 124/74 mm. No petechiae or evidences of peripheral emboli were found. There was no cyanosis. The tonsillar fossae were clean. The neck veins were not distended. A systolic thrill was palpable, strongest at the pulmonic area, but also present along the entire left sternal border. A suggestion of a diastolic thrill was felt over the pulmonic area. The heart seemed slightly enlarged. The sounds were normal, and the pulmonic second was well defined. There was a continuous "machinery" murmur at the pulmonic area, with both systolic and diastolic accentuation, becoming faintest at the end of diastole. The murmur was transmitted to a certain extent over the whole precordium.

The lungs were clear; the liver and spleen, not palpable. The fingers were not clubbed.

The hemoglobin was 76 per cent (Sahli), the erythrocytes, 4.2 millions; the leucocytes, 11,800 (81 per cent polymorphonuclears). The blood Wassermann reaction was negative. The urine was normal. Roentgenograms revealed slight cardiac

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enlargement with prominence of the left auricle and pulmonary conus. An electrocardiogram showed sinus tachycardia. Two blood cultures yielded *Streptococcus viridans.*

The diagnosis was made of congenital heart lesion (patent ductus arteriosus) and subacute bacterial endocarditis.

As the temperature subsided in a few days, the patient was dismissed with instructions to remain in bed. Subsequent care took place for the most part at her home. There were in all eleven hospital admissions, most of them of one or two days' duration for the purpose of blood transfusion.

Course.—For several months she seemed to hold her own before beginning a gradual decline, which became rapid in the final month. Her spirit, however, was high, and her will to get well strong until the very end.

There was almost constant septic fever, increasing as her condition grew worse. Daily temperature variations of as much as 5° C. were not uncommon in the later months. On one occasion the rectal temperature swung from 36.0° to 42.1° C., and back again within twenty-eight hours.

Death took place on July 8, 1932, a little more than a year after the onset of illness.

The only specific therapy attempted was a course of seven subcutaneous injections of autogenous vaccine, which had no apparent effect. She received a total of twenty blood transfusions as treatment both for the infection and for the anemia which developed rapidly in spite of vigorous iron therapy.

Beginning three months after the onset of the present illness, she had frequent attacks of chest pain with bloody sputum. These were thought to be due to pulmonary infarcts, although no physical signs of infarction could ever be elicited. A few attacks were followed by pleural effusions which did not require drainage. At no time were there any evidences of embolism in the peripheral circulation, although they were constantly looked for.

In April, 1932, nine months after the onset of the endocarditis, the spleen became palpable for the first time. At about the same time the fingers began to show clubbing. During the last months of illness the heart murmurs increased markedly in intensity without change in their character. The pulse never became rapid disproportionately to the temperature.

Blood.—The blood counts are detailed in Table I. It will be noted that the blood count was practically normal at onset but that anemia developed within two months. The series of twenty transfusions, each consisting of 500 c.c. of citrated blood, which were given in the ensuing nine months, were successful until the very end in preventing the anemia from becoming profound.

The results of the blood cultures are shown on Table II. Until the terminal flooding of the blood stream with organisms, the colonies in poured agar plates were small and appeared only after several days, even under partially anaerobic conditions.

Roentgenograms of the chest were repeated in October and again in April. In the first of these the cardiac enlargement was greater than it had been in July, and there was an extraordinary change in the size and shape of the heart shadow when the patient changed her position. This change was never satisfactorily explained and later ceased to occur. In April, the cardiac silhouette was still further enlarged. Many scattered, rather dense shadows not previously present were seen throughout the lung fields. These were interpreted as the remnants of infarcts.

Urine.—The urine remained perfectly normal until February (seven months after onset). In September, a faint trace of albumin was found at one examination, and an Addis concentration test was performed. This yielded the following results, all of which are within normal limts for twelve-hour excretion.

TABLE I

BLOOD COUNTS

DATE	HG. PER CENT (S.)	R.B.C. MILLIONS	W.B.C.	POLYS PER CENT	PLATELETS	RET. PER CENT
7/13/31	76	4.2	11,800	76		
9/19/31	55	3.8	20,400	85		
9/24/31			Transfusion I			
9/27/31	85	4.8	14,800	78		
9/28/31			Transfusion II			
10/ 1/31			Transfusion III			
10/ 5/31	95	5.4	12,200	81		
10/ 6/31			Transfusion IV			
10/ 7/31	95	5.4	----	--		
10/12/31			Transfusion V			
10/12/31	95	5.6	----	--		
10/20/31	92	4.9	10,800	69		
10/26/31	93	5.0	----	--		
11/ 1/31	88	4.7	10,800	52		
11/ 5/31	79	4.4	13,200	55	397,700	7.0
11/ 6/31			Transfusion VI			
11/ 7/31	97	5.4	11,100	73		
11/19/31	87	5.0	8,800	57		
12/ 1/31	77	3.7	7,700	--		
12/ 7/31	77	4.0	17,200	74		
12/ 7/31			Transfusion VII			
12/ 8/31	93	5.3	----	--		
12/18/31	86	5.0	13,200	77		
1/15/32	75	3.8	13,200	75		
1/15/32			Transfusion VIII			
1/16/32	86	5.1	----	--		
2/ 5/32	79	4.0	12,500	65		
2/26/32	58	3.6	11,600	81		
2/26/32			Transfusion IX			
3/16/32	59	3.3	22,800	72		
3/19/32			Transfusion X			
3/21/32	73	3.8	20,300	86		
3/21/32			Transfusion XI			
3/22/32	87	4.8	----	--		
3/26/32	81	4.1	11,000	72		
4/ 8/32	56	3.1	12,400	82		
4/ 9/32			Transfusion XII			
4/22/32	50	3.9	12,400	80		
4/22/32			Transfusion XIII			
4/23/32	60	4.1	14,000	73		
4/28/32			Transfusion XIV			
4/28/32	60	4.0	14,600	82		
5/ 6/32	58	3.6	15,000	85		

TABLE I—CONT'D

DATE	HG. PER CENT (S.)	R.B.C. MILLIONS	W.B.C.	POLYS PER CENT	PLATELETS	RET. PER CENT
5/ 6/32			Transfusion XV			
5/ 9/32	65	4.1	15,000	79		
5/11/32			Transfusion XVI			
5/11/32	72	4.1	----	--		
5/16/32	72	3.9	18,200	79		
5/23/32	55	3.6	17,800	62		
5/24/32			Transfusion XVII			
5/24/32	65	4.1	13,600	68		
5/28/32	60	3.8	25,400	69		
5/31/32			Transfusion XVIII			
5/31/32	69	4.1	------	--		
6/ 4/32			Transfusion XIX			
6/ 5/32	75	4.5	------	--		
6/ 6/32	77	4.7	23,200	88		
6/ 7/32	--	2.3	23,100	83		
6/ 7/32			Transfusion XX			
6/ 7/32	45	3.4	25,800	78	104,700	18.2

TABLE II

BLOOD CULTURES

DATE	GROWTH IN BROTH	PLATES COL. PER C.C. BLOOD
7/15/31	++	+
7/17/31	++	+
9/21/31	+	17
10/ 4/31	+	0
10/18/31	+	?
11/ 1/31	+	0
1/15/32	+	0
2/26/32	+	5
3/22/32	+	2
4/ 9/32	+	16
4/22/32	+	10
5/20/32	+	?
7/ 7/32	+++	830

Volume—102 c.c.
Specific gravity—1.032
Protein—7.4 mg.
Casts—5,600 (100 per cent hyaline)
Red blood cells—none seen
White and epithelial cells—1,500,000

In February, albumin, casts, red cells, and white cells began to make their appearance in voided specimens. A concentration test was obtained in May, with the following twelve-hour values:

Volume—220 c.c.
Specific gravity—1.015

Protein—570 mg.
Casts—1,300,000
Red blood cell casts—20 per cent
Epithelial casts—68 per cent
Granular casts—12 per cent
Red blood cells—106,000,000
White and epithelial cells—260,000,000

These figures Dr. Addis interpreted as indicating an active hemorrhagic nephritis with marked degeneration of the tubules.

In June, edema of the ankles, soft and pitting, made its appearance. On salt restriction this diminished temporarily, but progressed within a few weeks to a generalized anasarca. At her final admission in July, the urine boiled solid and was loaded with formed elements, but the blood urea was only 45 mg. per 100 c.c. of blood.

Mode of Death.—During the final month, while the edema was spreading, she appeared to lose ground rapidly. She lost her appetite, became fretful, and was racked by cough productive of pinkish watery sputum, apparently the result of mild pulmonary edema. A few days before death, purpura appeared over the antecubital fossae. This became confluent and spread over almost the entire body. She gradually became lethargic and cold, and finally ceased breathing, apparently the victim of bacterial toxemia rather than of cardiac or renal failure.

Post-Mortem Examination.—The body was that of a slender girl about nineteen years old. The body was warm, rigor mortis absent. The pupils were dilated and equal. The conjunctivae were pale and clear. The skin and mucous membranes showed a marked pallor. Numerous petechial hemorrhages and extensive areas of purpura were present over the lateral aspects of each arm and upper portion of the forearm. A few small petechiae were scattered over the right thigh and left leg. Small hemorrhagic spots were present in the adventitia at the base of the aorta, in the epicardium over the right auricular appendage, and at the base of the pulmonary artery. A diffuse purpuric infiltration was present in the gastric mucosa and in the bladder. Small purpuric areas were present in the cecum.

A moderate pitting edema of both extremities was present. The subcutaneous tissues over the thorax and abdomen also showed moderate edema.

The peritoneum was smooth, glistening, and contained approximately 400 c.c. of thin, slightly turbid, blood-tinged fluid. The pleurae were free of fluid. The pericardial sac contained 200 c.c. of clear, straw-colored fluid.

The left lung showed no scar at the apex. Both lobes contained numerous infarcts, varying in size from 1 to 3 cm. in diameter. Some were partially organized, others were of recent origin. The right lung showed a scar at the apex. Throughout all three lobes numerous infarcts of various size and age were present. The bronchi contained a small amount of frothy, blood-tinged mucus. The peribronchial and peritracheal nodes were moderately enlarged and edematous. The spleen was moderately enlarged, measuring 16 by 11 by 8 cm. The capsule was smooth and bluish brown in color. On cut section the malpighian bodies were prominent, and the pulp was firm and of a dark, reddish brown color.

The heart appeared about twice normal size. Both right and left ventricles were dilated. The ventricular muscle was of normal thickness, rather pale and flabby. The right ventricular wall measured 3 mm. in thickness, the left 10 mm. in thickness. Mural vegetation measuring 1.5 by 1 by 0.8 cm. was present on the endocardium of the right ventricle, 6 cm. from the pulmonary valve, and near the insertions of the chordae tendineae of the tricuspid valve. All the valves were normal except the pulmonary. The pulmonary ring measured 7 cm. in circumference. The leaflets were completely destroyed except at the bases where they were thin and delicate. Extending from a point just beneath the valve and into the pulmonary artery for

a distance of 3 cm., was a cauliflower-like mass of yellowish vegetations which presented a pale greenish tint in addition to the yellow color. Upon opening the valve it appeared as though the orifice was completely occluded by these vegetations. A patent ductus arteriosus was present. The pulmonary end was at a level 5 cm. distal to the base of the pulmonary valve. Projecting outward from the lumen of the ductus was a small polypoid mass of similar yellowish green vegetations measuring 1 by 0.8 by 0.7 cm. A moderate dilatation of the pulmonary artery was present. The lumen of the ductus arteriosus was almost completely occluded by vegetations and measured from 2 to 3 mm. in diameter (see Fig. 1). On the aortic side of the ductus two small polypoid vegetations were present. No calcified plaques were noted in the aorta.

Both kidneys measured 11 by 5 by 3.5 cm. The perirenal tissues showed moderate edema. Both renal capsules stripped rather easily. The renal surfaces were congested, brownish red in color, speckled diffusely by numerous small hemorrhages, pinpoint in size, ranging in color from dark brown to bright red. Between the

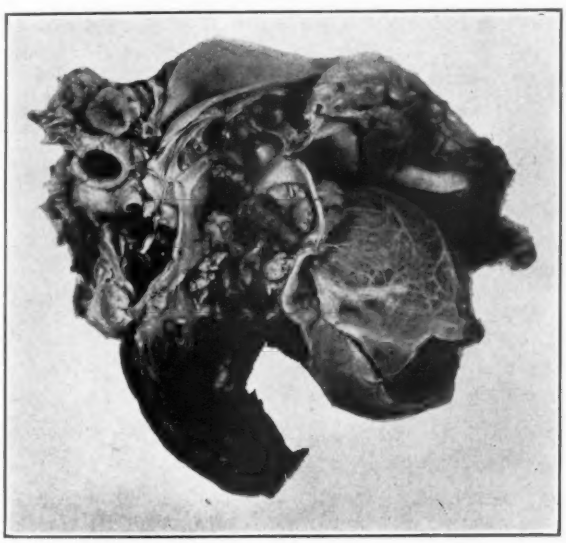

Fig. 1.—Right ventricle of heart. Note the mural vegetation, the cauliflower-like mass of vegetation on the pulmonary valve, and the vegetations on the pulmonic side of the ductus arteriosus. A match is inserted in the orifice of the ductus arteriosus.

hemorrhagic areas numerous small yellowish areas were present. Cut section showed in addition a moderate edema and a moderate cloudy swelling. The mucosa of the renal pelvis was pale, smooth, and glistening.

Histological Examination.—The heart muscle was normal in appearance.

The liver showed a marked congestion throughout. The central sinusoids were considerably widened. The neighboring liver cells were slightly atrophic, contained small amounts of brown granular pigment, and showed a slight fatty degeneration. Some of the periportal areas showed small collections of lymphocytes.

The peribronchial lymph nodes contained a number of large mononuclear phagocytes filled with brown granular pigment in the lymph sinuses.

Sections of the lungs showed infarcts of varying ages. A number of the alveoli were filled with plasma containing scattered numbers of large mononuclear phagocytes.

The skin of the arm showed numerous small hemorrhages into the areolar tissue in the depth of the corium at the level of the coil glands.

The stomach showed a marked congestion of the mucosa and a hemorrhagic infiltration of the superficial portion.

In the kidneys a number of glomeruli showed necrosis of individual capillary loops. Other glomeruli showed an exudation of coagulated material in Bowman's capsule. A few glomeruli showed frank hemorrhage, with numerous blood casts contained in the neighboring tubules. In addition to the above embolic glomerular changes, a number of the glomeruli showed adhesions between the tufts and the neighboring epithelium of Bowman's capsule. A few showed beginning formation of epithelial crescents. The tubules were of varying size, some being small and atrophic. Numerous hyaline, epithelial, and cellular casts were contained therein. Small groups of lymphocytes were scattered throughout the cortex. The arteries appeared essentially normal.

Bacteriological Examination.—The blood culture showed a growth of *Streptococcus viridans,* alpha (Brown).

Anatomical Diagnoses.—The anatomical diagnoses were: open ductus arteriosus; subacute arteritis of the ductus arteriosus; subacute endocarditis of the pulmonary valve; septicemia (*Streptococcus viridans*); embolism of the pulmonary artery with multiple infarcts in the lungs; early subacute nephritis; acute, focal, embolic nephritis; purpura hemorrhagica, and secondary anemia.

DISCUSSION

Two points of especial interest are presented by this case: (1) the infective process at the site of the congenital anomaly and (2) the renal lesion. Adequate discussion of the first of these points is found in the reviews previously cited,[1] and we shall simply point out that here the endocardial lesions were limited to the ductus, the pulmonary artery, the pulmonic valve, and the wall of the right ventricle. In spite of the multiple infarctions of the lungs and the protrusion of vegetations from the ductus into the aorta, no systemic infarctions were found.

The onset of nephritis early in 1932 was not accompanied by clinical signs or symptoms. The patient noted nothing peculiar about the urine, and there was no edema. The sudden onset of edema in June was not accompanied by evidence of renal failure.

Clinically, the renal lesion was a typical active hemorrhagic nephritis. Pathologically, there was present a diffuse glomerulonephritis as well as the focal embolic type of lesion first described by Löhlein[3] and Baehr.[4] The interesting discussion of such lesions by Addis and Oliver[5] cannot be supplemented here.

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Department of Reviews and Abstracts

Selected Abstracts

Segal, Maurice S.: Auricular Fibrillation and Auricular Flutter in the Course of Subacute Bacterial Endocarditis. New England J. Med. **212**: 1077, 1935.

A review of 192 cases of bacterial endocarditis revealed two cases of auricular flutter and three cases of auricular fibrillation in the course of subacute bacterial endocarditis. One case of auricular fibrillation appeared in the course of acute bacterial endocarditis. The case reports with autopsy protocols and additional case reports from the literature are included.

The cases of auricular fibrillation or flutter occurring in the course of active subacute bacterial endocarditis all showed evidence of mitral valve involvement alone or in combination with the aortic valve.

In the cases of fibrillation or flutter, when the mitral valve was involved by the vegetations, there was found either a normal mitral orifice, mitral regurgitation, or moderate mitral stenosis. No cases of severe mitral stenosis were found. The circumferences of the mitral orifices ranged from 9.5 cm. through 15 cm.

Terminal circulatory failure was found in 50 per cent of the cases of auricular fibrillation or flutter in the course of subacute bacterial endocarditis.

The rare incidence of auricular fibrillation in the course of active subacute bacterial endocarditis cannot be attributed entirely to the rare incidence of severe mitral stenosis in this disease.

The integrity of the myocardium and the underlying physiological and biological state would appear to be more closely related to the pathogenesis of auricular fibrillation than the grade of mitral stenosis per se.

Baker, Roger Denio: Endocardial Tuberculosis. Arch. Path. **19**: 611, 1935.

Endocardial tuberculosis is not uncommonly encountered at necropsy, most frequently as a part of generalized miliary or disseminated tuberculosis. Scattered tubercles from microscopical size to a diameter of 3 or 4 mm. may occur in any part of the endocardium, including the valves. They probably arise by implantation through the coronary arteries and directly from the blood of the heart. Rarely they may be polypoid or pedunculated.

Endocardial tuberculosis may also develop from the extension inward of pericardial and myocardial caseous masses, which may ulcerate and produce generalized tuberculosis. With staining for elastic tissue, it can be shown that a myocardial tuberculous process bulging into the cavity of the heart but apparently covered with a smooth endocardial surface is in some cases really invading the endocardium.

A convincing report of tuberculous endocarditis as a diffuse process at the line of closure of the valves, somewhat analogous to rheumatic and pyogenic endocarditis, has occurred in the literature possibly once. In general, however, tuberculosis has no especial affinity for the line of closure and does not produce thrombotic vegetations.

Endocardial tuberculosis may interfere with cardiac function in the rare instances in which caseous nodules involve the valves.

Sclerosis of the endocardium and healed fibrous or calcified valvular lesions noted at autopsy were not shown to be due to the toxic action of a tuberculous process elsewhere in the body.

Bryan, A. Hughes, Evans, William A., Jr., Fulton, Marshall N., and Stead, E. A., Jr.: Diuresis Following the Administration of Salyrgan: Its Effect on the Specific Gravity, the Total Nitrogen and the Colloid Osmotic Pressure of the Plasma of Normal and of Edematous Dogs. Arch. Int. Med. **55**: 735, 1935.

Studies are reported concerning the effect of the diuresis following the administration of salyrgan on the specific gravity and the colloid osmotic pressure of the plasma in normal dogs and on these same factors plus the total nitrogen content of the plasma in dogs made edematous by plasmapheresis and by the feeding of salt and a low protein diet.

When salyrgan alone was administered to normal dogs, the diuretic response was slight and was not accompanied by any significant changes in the plasma specific gravity or in the colloid osmotic pressure.

Following the administration of water by mouth, a fall occurred in the measurements which was not significantly altered when water and salyrgan were administered together.

In edematous dogs salyrgan produced a marked and prolonged diuresis. No significant changes were observed in the specific gravity, the total nitrogen content, or the colloid osmotic pressure of the plasma before the onset of diuresis. Coincident with the diuresis, however, a sustained rise in all of these values occurred.

The findings are discussed in relation to current theories of the action of salyrgan as affording no evidence of an extrarenal action and indicating predominantly a direct effect on the kidney.

Stroud, W. D., Livingston, A. E., Bromer, A. W., VanderVeer, J. B, and Griffith, G. C.: The Use of Verodigen (a Digitalis Glucoside) in Cardiovascular Disease, Its Biological Assay, and Pharmacological Action. Ann. Int. Med. **8**: 710, 1934.

A clinical study of the therapeutic efficiency of verodigen—the gitalin glucoside of digitalis—has been made upon: (a) five patients with established auricular fibrillation and one patient with auricular flutter, previously untreated with digitalis; (b) two patients with regular sinus rhythm and advanced congestive heart failure; (c) fourteen patients with established auricular fibrillation, previously controlled with whole leaf digitalis preparations or digalen.

Verodigen was found to control the ventricular rate in established auricular fibrillation; to produce clinical improvement, with marked diuresis, in patients with congestive heart failure and regular sinus rhythm; and to produce in the electrocardiogram S-T interval and T-wave changes, characteristic of digitalis action.

Careful clinical observation revealed $\frac{1}{240}$ grain of verodigen to be equivalent to one cat unit (approximately $1\frac{1}{2}$ grains of powdered digitalis leaves).

The total dosage necessary for optimum digitalization varied from $\frac{1}{10}$ to $\frac{1}{16}$ grain, administered over a period of five to six days.

The most frequent adequate maintenance dose of verodigen was $\frac{1}{240}$ grain daily.

Toxic effects from overdosage with verodigen were similar to those produced by whole leaf digitalis preparations.

The potency of verodigen demands careful observation in its administration, especially with patients who have recently been taking any digitalis preparations.

Spink, Wesley W.: Cardiovascular Complications of Trichinosis, Arch. Int. Med. **56:** 238, 1935.

Acute myocarditis occurring in trichinosis may be a nonspecific inflammatory reaction due to the invasion of the myocardium by larvae.

A review of the literature shows that other cardiovascular manifestations include congestion and hemorrhage of the eyes, lungs and gastrointestinal tract; edema; thrombosis; embolism with infarction; and hypotension.

Six of eighteen cases of trichinosis (33.3 per cent) showed electrocardiographic changes. These changes included an initial flattening or inversion of the T-wave, especially in Lead II, the wave subsequently becoming upright; low amplitude of the QRS complex, and intraventricular block.

The postmortem changes in a fatal case of trichinosis with myocarditis are presented. Another case is recorded in which trichinosis was complicated by a permanent right hemiplegia.

Burwell, C. S., and Flickinger, D.: Obstructing Pericarditis: Effect of Resection of the Pericardium on the Circulation of a Patient With Concretio Cordis, Arch. Int. Med. **56:** 250, 1935.

A case is reported in which a high degree of obstructing pericarditis was present. This pericarditis was due to infection of the pericardium with *Staphylococcus aureus.* Removal of a portion of the pericardium was followed by a fall in venous pressure, a rise in cardiac output and an increase in pulsation of the heart. Increased venous pressure and decreased cardiac output appear to be the chief mechanisms underlying the symptoms and signs of concretio cordis.

Koucky, J. D., and Milles, G.: Stab Wounds of the Heart: A Study of Electrocardiographic Changes, Polyserositis and Pericarditis, Arch. Int. Med. **56:** 281, 1935.

A case of stab wound of the heart with recovery is reported.

Complete electrocardiographic studies and their comparison with similar studies show that a Pardee curve, replaced after about ten days by an inversion of the T-wave, occurred in all cases. A complete return to the normal curve is the rule.

Our case was complicated by polyserositis, which may have resulted from the use of surgical solution of chlorinated soda in irrigating the pericardial sac after the development of pericarditis. The mechanism of the development of polyserositis is discussed.

Roentgenographic visualization of the pericardial sac after injection of an iodized and chlorinated peanut oil was carried out. The pictures disclosed little obliteration of the pericardial sac.

The operation performed without anesthesia or anything more than the most cursory attempts at sterility, necessitated by the extreme state of the patient, resulted in ultimate and complete recovery.

Bernstein, Alan: Periarteritis Nodosa Without Peripheral Nodules Diagnosed Antemortem, Am. J. M. Sc. **190:** 317, 1935.

A fatal case of periarteritis nodosa without peripheral nodules, suspected and proved by biopsy antemortem, is recorded. The patient's illness was characterized by weakness, emaciation, fever, peripheral neuritis, abdominal pain, edema, occlusion of a central retinal artery, deafness, vacillating hypertension, tachycardia, anemia with leucocytosis and eosinophilia, and changes in the urine. The Wassermann reaction was positive. Potassium iodide failed to arrest the progressive course of the disease.

Mention is made of six other cases of periarteritis nodosa in the files of this hospital. One of these was diagnosed at autopsy; a second, at laparotomy. The last four were recognized by searching through the autopsy material of the department of pathology.

The significance of some of the symptoms and signs encountered in periarteritis nodosa is appraised. Reasons are offered to indicate that the disease may not be quite as uncommon as the paucity of recognized cases would lead one to believe.

Krahulik, L., Rosenthal, M., and Loughlin, H. E.: Periarteritis Nodosa (Necrotizing Panarteritis) in Childhood With Meningeal Involvement, Am. J. M. Sc. **190:** 308, 1935.

1. A case of necrotizing panarteritis (periarteritis nodosa) in a girl, aged nine years, is presented.

2. The widespread vascular lesions correspond to the degenerative, inflammatory and granulation tissue stages of this disease, as described by Arkin.

3. A primary subacute leptomeningitis due to periarteritis nodosa is described. No other cases of primary meningitis either in children or adults have been reported.

4. The occurrence of unusual features, such as gastrointestinal ulceration with perforation and peritonitis, ulceration of the skin following injury, and the occurrence of ocular lesions has been briefly discussed.

Middleton, W. S., and McCarter, J. C.: The Diagnosis of Periarteritis Nodosa, Am. J. M. Sc. **190:** 291, 1935.

From this review of the subject certain deductions regarding periarteritis nodosa seem reasonable:

1. The incidence of the disease probably greatly exceeds its recognition clinically and pathologically.

2. The pathology consists of a necrotizing arteritis, subacute and chronic cellular and fibrinous exudation, aneurysm formation, thrombosis, and fibroblastic proliferation and repair. The smaller arteries and arterioles are affected; and degeneration and infarction in the areas of supply are common.

3. Etiologically periarteritis nodosa is probably closely associated with the "rheumatic group" of diseases.

4. The tetrad of Meyer and Brinkmann, chlorotic marasmus, polyneuritis and polymyositis, striking abdominal manifestations (cramps, vomiting, diarrhea, melena and perforation), and nephritis, offers a logical foundation for the clinical appreciation and diagnosis of periarteritis nodosa.

5. Unexplained fever, polymyositis, polyneuritis, and eosinophilia constitute peculiar grounds for the consideration of this diagnosis.

6. Wherever the question arises, recourse should be had to biopsy of accessible nodules or voluntary muscle.

7. Further study may grant diagnostic values to ophthalmoscopy, electrocardiography, and roentgenography of the lungs in periarteritis nodosa, as yet not clearly established.

Friedman, Ben, Resnik, H. Jr., Calhoun, J. A., and Harrison, T. R.: Effect of Diuretics on the Cardiac Output of Patients With Congestive Heart Failure, Arch. Int. Med. **56:** 341, 1935.

Diuretic drugs, even when administered to patients with minimal edema, often produce marked relief from dyspnea. The vital capacity is frequently increased following their administration.

Constant effects on the cardiac output have not been observed following the administration of these drugs. Occasionally the output is diminished. This effect is believed to be due to loss of peripheral edema, for the blood supply of edematous tissues is, in proportion to their metabolic needs, often relatively greater than the blood supply to the tissues in general. In some instances the cardiac output is increased by diuretic drugs. This effect is believed to be dependent on an action of these drugs on the heart and possibly to be related to loss of edema from the cardiac musculature. In many instances the administration of diuretic drugs is followed by no demonstrable change in the cardiac output. In such instances it is believed that the peripheral and cardiac actions of the drugs tend to neutralize each other. In favorable circumstances diuretic drugs appear to cause benefit both by tending to decrease the load on the heart and by increasing the ability of the heart to carry its load.

The foregoing evidence is interpreted as indicating that diuretic drugs are of more than symptomatic value. They should be employed frequently for ambulatory patients who have minimal edema or who are suspected of having latent edema.

Riseman, J. E. F., Gilligan, D. R., and Blumgart, H. L.: Treatment of Congestive Heart Failure and Angina Pectoris by Total Ablation of the Normal Thyroid Gland: The Sensitivity of Man to Epinephrine Injected Intravenously Before and After Total Thyroidectomy, Arch. Int. Med. **56:** 38, 1935.

Studies of the sensitivity of the cardiovascular system of man to injections of epinephrine before and after total thyroidectomy are presented.

Three aspects of the physiologic action of epinephrine have been studied: (1) the sensitivity to epinephrine injected intravenously in patients with normal cardiovascular systems, angina pectoris or chronic cardiac failure; (2) the sensitivity to epinephrine of patients with various levels of basal metabolism; and (3) the rôle played by sensitivity to epinephrine in the improvement which occurs following total ablation of the thyroid gland in patients with angina pectoris or chronic heart disease.

Dilute solutions of epinephrine of known concentrations were injected by constant intravenous drip, and the responses of the blood pressure, heart rate, respiratory rate and depth, consumption of oxygen, and blood sugar content were measured. Eighty-six studies were made in seventeen subjects.

The intravenous administration of epinephrine was followed by a definite and characteristic increase in the systolic blood pressure, heart rate, consumption of oxygen of the body, rate and depth of respiration, and blood sugar content. The changes in diastolic blood pressure were variable and not great.

The responses to a given amount of epinephrine injected intravenously were strikingly similar when repeated measurements were made in a given subject under controlled conditions. The responses varied from person to person.

The response of the systolic blood pressure was closely related to the rate of injection of epinephrine and was found to be the most valuable single index of the patient's sensitivity to epinephrine. The changes in heart rate, diastolic blood pressure, consumption of oxygen, and measurements of respiration were not as directly related to the dose of epinephrine. Patients with angina pectoris and those with congestive heart failure were not more sensitive to epinephrine than patients with no evidences of cardiovascular pathologic changes.

The sensitivity to epinephrine as measured by the aforementioned generally accepted indices remained unchanged after total thyroidectomy so long as the basal metabolic rate was not lower than minus 30 per cent and the patient was free from distressing symptoms of myxedema.

When marked myxedema developed and the basal metabolic rate decreased below minus 30 per cent, a decreased response of the blood pressure and the heart rate to epinephrine became manifest in some instances.

The results of the present investigation show that the clinical improvement which followed total ablation of the normal thyroid gland is independent of any changes in the sensitivity to epinephrine, no alteration in the response to epinephrine being evident at the levels of hyperthyroidism maintained in our patients after operation.

Observations are presented which provide additional evidence that the relief from pain experienced by patients with angina pectoris immediately after total thyroidectomy, when there is no change in the basal metabolic rate or in sensitivity to epinephrine, is due to the interruption of sensory impulses from the heart to the central nervous system.

Duff, G. L.: Experimental Cholesterol Arteriosclerosis and Its Relationship to Human Arteriosclerosis, Arch. Path. **20**: 259, 1935.

Arterial lesions which resemble those of human arteriosclerosis can be produced in rabbits by the administration of diets containing considerable quantities of cholesterol. I have chosen to call this experimental disease of the arteries "experimental cholesterol arteriosclerosis." The literature bearing on experimental cholesterol arteriosclerosis is reviewed in detail. The results of attempts to produce arterial lesions by cholesterol feeding in animals other than rabbits are described. The data which have arisen from all of these experiments are summarized briefly in Section VII of this paper.

On the basis of these data, the etiology and pathogenesis of experimental cholesterol arteriosclerosis in the rabbit are discussed. It is concluded that the presence of considerable quantities of cholesterol in the diet with a resulting elevation of the level of cholesterol and other lipoids in the blood is essential to the development of the typical arterial lesions in rabbits. It is shown, however, that hypercholesteremia alone cannot be regarded as the cause of the lesions in the arteries. There are preliminary local alterations in the walls of the arteries which precede the precipitation of lipoids. Evidence is advanced to show that these preliminary changes are due to some form of injury to the arteries attendant on the experimental procedure of cholesterol feeding. It is concluded that the occurrence of local changes in the arterial walls, due in all probability to injury of some kind, is the primary event in the development of the lesions of experimental cholesterol arteriosclerosis, an event which is followed subsequently by the precipitation of lipoids in the injured areas.

As a preliminary to the discussion of the significance of the experimental results, a comparison is drawn between the anatomic lesions of experimental cholesterol arteriosclerosis and those of human arteriosclerosis. It is demonstrated that the two diseases are not identical and that there are a number of important differences between them. These differences are of such a nature as to suggest strongly that the rôle of the lipoids in the development of arteriosclerosis as compared with arteriosclerosis in man. A number of normal differences between the rabbit and man which render interpretation difficult and uncertain are pointed out. It is shown that the experimental data are not capable of accurate interpretation without recourse to data on corresponding points derived from the study of human material. With this fact in mind, an attempt is made to correlate the data concerning experimental cholesterol arteriosclerosis with the available information regarding human arteriosclerosis. The three main factors which can be recognized in the etiology of experimental cholesterol arteriosclerosis, namely, cholesterol in the diet, hypercholesteremia, and injury to the arteries, are considered in order as regards their possible signif-

icance in the etiology of human arteriosclerosis. With full cognizance of the inferences which have been drawn in the past from the experimental results, the following conclusions are reached for reasons which are given in their appropriate places:

The results of cholesterol feeding experiments in rabbits do not constitute a valid reason for believing that an excess of cholesterol in the diet plays any rôle in the etiology of arteriosclerosis in man. No convincing evidence in support of such a belief exists at present.

Hypercholesteremia is not found with any regularity in association with human arteriosclerosis. It seems highly probable that arteriosclerosis in man can and usually does develop without deviation of the cholesterol content of the blood beyond the normal limits of variation. In any event, there is no valid evidence to support any other conclusion.

Hypercholesteremia of itself cannot be regarded as a cause of human arteriosclerosis. Although hypercholesteremia, when it occurs, might be expected on theoretical grounds to accelerate the development of arteriosclerotic changes which have already been initiated, there is little evidence at present to indicate the existence of such an effect.

The cholesterol feeding experiments provide no valid reason for believing that a disturbance of cholesterol or lipoid metabolism plays any part in the etiology of human arteriosclerosis. There is no definite or concrete evidence from observations on human beings to support the idea. If a disturbance of lipoid metabolism participates in the etiology of arteriosclerosis in man, the fact remains to be demonstrated in the future.

The initial stage in the development of human arteriosclerosis consists of local changes in the walls of the arteries themselves, changes which are responsible for the subsequent precipitation of lipoids in the affected areas. In man, as in the rabbit, there is every reason to believe that these changes follow as the result of some sort of injury to the arterial walls. As to the cause of this injury, the experimental data yield hardly any information which is capable of application in the human being. Some possible causes of the arterial injury which have been suggested previously and on which the experimental results have some bearing are discussed briefly. Brief comment is also made on the influence of age. No definite conclusions are reached, since it is clear that the cause of the injury to the arteries which is responsible for the development of human arteriosclerosis is unknown.

Following the initial local injury, lipoids are deposited in the injured intima, especially in the intercellular substances. These deposits stir into activity numerous macrophages whch are attracted to the site and which then engulf a large part of the lipoid material. It seems entirely probable that the free lipoid deposits can stimulate the proliferation of connective tissue cells in the intima. This effect is added to that of the original injury to produce a reparative fibrous tissue reaction in the affected areas. If the original injury which initiated the whole process ceases to operate, it is probable that the lipoid deposits prevent immediate healing and continue to exert their influence so that the lesions persist, progressing slowly. Under these conditions, however, it seems likely from the experimental evidence that the lipoids may be slowly removed and may even disappear finally, leaving only a fibrous thickening of the intima. It is unnecessary to assume that a disturbance of cholesterol or lipoid metabolism plays a part in any stage of the process.

This outline of the development of human arteriosclerosis is entirely consistent with the knowledge derived from the study of arteriosclerosis in man, and at the same time it incorporates those inferences which can be drawn with justification from the experimental data. It seems to be the most reasonable working hypothesis which can be constructed from the evidence available.

A tentative scheme of the relationship between experimental cholesterol arteriosclerosis and human arteriosclerosis is offered, which explains in a logical way the apparent discrepancies between the conclusions which have been drawn in this paper regarding the two diseases.

Margolies, A., Rose, E., and Wood, F. C.: The Heart in Thyroid Disease: The Effect of Thyroidectomy on the Orthodiagram, J. Clin. Investigation 14: 483, 1935.

1. Significant increase in cardiac area occurs frequently in uncomplicated hyperthyroidism (26 per cent of our cases). The incidence of such increase in patients with uncomplicated nontoxic goiter is also probably abnormal (14 per cent in our series of 28 cases).

2. Following thyroidectomy in uncomplicated hyperthyroidism, there is a tendency for hearts of abnormal size, whether large or small, to return toward normal and for hearts within the normal zone to remain so. This tendency is not materially affected by failure to control completely the hyperthyroidism.

3. Significant changes in cardiac area do not occur following thyroidectomy for uncomplicated nontoxic goiter.

4. Postoperative hypothyroidism may occasionally be a factor in increasing cardiac area.

5. Temporary variations in cardiac area, without significant ultimate changes, occur after thyroidectomy for uncomplicated hyperthyroidism in some cases (19 per cent in our series). The cause of these variations is not known.

6. Congestive heart failure in hyperthyroidism is almost always accompanied by enlargement of the cardiac area. This tends to decrease with postoperative restoration of compensation, provided the thyrotoxicosis is also relieved.

7. Increased prominence and/or pulsation of the pulmonary artery is frequent in hyperthyroidism (54 per cent of our cases). It occurs less frequently in association with nontoxic goiter (14 per cent of our cases). The cause of these changes is unknown. We were unable to demonstrate any relation between them and (a) changes in heart size, (b) systemic blood pressure, (c) preoperative heart rate, or (d) basal metabolism, in patients with toxic or nontoxic goiter. In about three-fourths of our cases, the abnormality of the pulmonary artery disappeared within one to seven months after thyroidectomy.

8. Cardiac pulsation, as observed fluoroscopically, is usually characteristically altered in hyperthyroidism.

9. The heart (exclusive of the vascular pedicle) does not assume a characteristic shape in persons with toxic or nontoxic goiter.

Rose, E., Wood, F. C., and Margolies, A.: The Heart in Thyroid Disease: The Effect of Thyroidectomy on the Electrocardiogram, J. Clin. Investigation 14: 497, 1935.

1. Abnormal electrocardiograms occur with about the same frequency in patients with toxic and nontoxic goiter (45 and 41 per cent, respectively, in our series).

2. Changes in normal electrocardiograms after partial or subtotal thyroidectomy are more common in patients with hyperthyroidism than in those with nontoxic goiter (97 per cent as compared with 56 per cent in our series).

3. Large P-waves (3 mm. or more in height) are common in hyperthyroidism. They are usually reduced to less than 3 mm. after successful thyroidectomy.

4. Following partial or subtotal thyroidectomy in hyperthyroidism, the electrical axis of the heart shifts to the left in about half the cases. The cause of this shift is unknown; it is apparently not due to changes in body weight alone.

5. Marked T-wave changes occur before and after thyroidectomy in hyperthyroidism, but they follow no apparent pattern, and their occurrence is unpredictable. The T-waves in hyperthyroidism are not characteristically larger than normal, nor do they necessarily become reduced in size when the hyperthyroidism is relieved.

6. T-wave inversion in thyrotoxicosis does not necessarily indicate the presence of chronic myocardial disease. It occurs quite frequently as a transient phenomenon.

7. The electrocardiographic changes seen in patients with toxic and nontoxic goiter do not seem to be related to (a) changes in heart size, (b) heart rate, (c) postoperative improvement in thyrotoxicosis, (d) duration or severity of thyrotoxicosis, (e) age, (f) sex, (g) the state of cardiac compensation, (h) the presence of substernal goiter, (i) operative injuries to the recurrent laryngeal nerve, (j) the type of anesthesia employed, or (k) the severity of the postoperative reaction.

Altschule, Mark D., and Vook, Marie C.: The Minute Volume Output and the Work of the Heart in Hypothyroidism, J. Clin. Investigation **14:** 385, 1935.

1. The minute volume output and the work of the heart are greatly diminished in hypothyroidism following total ablation of the normal thyroid gland.

2. The cardiac output decreases progressively more rapidly than the oxygen consumption as the basal metabolic rate falls in hypothyroidism. This disproportionate decrease in cardiac output is accompanied by a progressive increase in the arteriovenous difference.

3. In most instances the velocity of blood flow was decreased when the cardiac output was low. In some instances, however, the velocity of blood flow did not reflect accurately the work of the heart.

4. The venous pressure, arterial pressure, and vital capacity were not significantly altered after total thyroidectomy in the patients of this series.

Arnett, John H.: Vital Capacity of the Lungs: Changes Occurring in Health and in Disease, J. Clin. Investigation **14:** 543, 1935.

1. The vital capacity in two consecutive years was determined in a group of 482 youthful healthy subjects. Deviations from the readings of the previous year proved to be decidedly smaller than those from the hypothetical vital capacity as calculated from the surface area formula of West. The reading of the previous year, therefore, constituted the more reliable basis for vital capacity prediction.

2. In a group of seventy-four cases of acute bronchitis an average diminution from the previously determined healthy figure was noted in both ambulatory and bed cases, a more marked diminution occurring in the latter.

3. The vital capacity is shown before, during, and after illness, in cases of pneumonia, spontaneous pneumothorax, and cardiac decompensation. These observations are believed to be unique.

Boas, E. P.: Angina Pectoris and Heart-Block as Symptoms of Calcareous Aortic Stenosis, Am. J. M. Sc. **190:** 376, 1935.

The syndrome of angina pectoris is common in patients with aortic stenosis. It appears to be caused, not by disease of the coronary arteries, but by the narrowing of the aortic valvular opening itself, which impairs the blood supply to both coronary arteries simultaneously. Sudden heart failure in these patients is often followed by symptoms simulating coronary thrombosis.

Auriculoventricular conduction disturbances are also often associated with the calcific form of aortic stenosis. These are determined by extension of the calcific

process into the annulus fibrosus, or ventricular septum. At times a secondary infection of the diseased valve causes heart-block by direct extension into the auriculoventricular bundle. Isolated aortic stenosis is probably of rheumatic origin.

Shambaugh, Philip: Circulatory Changes in Angina Pectoris, Arch. Int. Med. 56: 59, 1935.

Experimental evidence is presented to show that in the dog cardiac pain produced by mechanical constriction of the coronary vessels does not cause a significant rise in blood pressure. On the other hand, the pain response can be precipitated by suddenly raising the blood pressure in the presence of a subminimal constriction of the coronary vessels.

Wolferth, Charles C., Wood, F. C., and (collab.) Bellet, S.: Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of Left Ventricle, Arch. Int. Med. 56: 77, 1935.

A group of ten cases is reported in which the electrocardiographic evidence pointed to recent infarction of both the anterior and the posterior wall of the left ventricle. Permission for necropsy was obtained in two of the cases. In each instance an infarct was found involving the lower part of the anterior wall, the apex, and the lower part of the posterior wall.

The electrocardiographic findings were as characteristic as those of recent infarction limited to the anterior or the posterior wall.

The recognition of the signs of acute involvement of both the anterior and the posterior wall removes a source of confusion in the electrocardiographic localization of myocardial infarction.

Chavez, I., and Carvallo, J. M. R.: A New Method for Differentiation of Aortic and Pulmonary Murmurs, Arch. latino am. de cardiol. y hemat. 5: 115, 1935.

The authors describe a method which allows the differentiation of aortic murmurs from pulmonary murmurs, which is useful, chiefly in cases in which the blood pressure, x-ray pictures, etc., are not enough to reach this differentiation.

The method consists in studying the changes undergone by the murmurs under the influence of forced inspiration and expiration and of postinspiratory and postexpiratory apnea.

1. Forced inspiration and postinspiratory apnea produce muffling of the heart sounds and murmurs, especially in the base, with the exception pointed out in the fourth conclusion.

2. Forced expiration and postexpiratory apnea, on the contrary, frankly reinforce all the acoustic phenomena of the heart chiefly in the base.

3. For better appreciation of these phenomena in the base of the heart, the authors recommend the left lateral decubitus combined with the postexpiratory apnea, which are for the phenomena of the base what the Pachon's decubitus is for those of the apex.

4. Systolic murmurs of the pulmonary artery, against the general rule, are frankly reinforced by forced inspiration and postinspiratory apnea while systolic murmurs of the aorta are muffled by the same, a fact which allows their differentiation.

5. Diastolic murmurs of the pulmonary artery are reinforced with forced expiration and postexpiratory apnea in a greater degree than the diastolic murmurs of the aorta which are moderately reinforced.

6. The reason for the reinforcement of the pulmonary systolic murmurs seems to be increase of blood flow through the pulmonary artery during forced inspiration.

Cossio, Dres P., and Berconsky, I.: Coexistence of Syphilitic Aortic Insufficiency and Rheumatic Mitral Disease, Rev. argent. de cardiol. **2:** 37, 1935.

The case is reported of a man forty-three years old who contracted rheumatic fever when twenty-eight and syphilis when thirty-five years old. On the basis of the clinical, radiological, and electrocardiographic study, a diagnosis of aortic insufficiency and mitral disease was instituted. The etiological diagnosis offered some difficulties on account of the two heart-affecting diseases that the patient suffered. A syphilitic aortic process and rheumatic mitral process were finally accepted. The autopsy confirmed both anatomical and etiological diagnoses made when the patient was alive. The association of a rheumatic mitral disease with a syphilitic aortic insufficiency is an exceptional one.

Cossio, Dres P., and Menendez, E. B.: Phonocardiographic Studies of Total Auriculoventricular Block, Rev. argent. de cardiol. **2:** 1, 1935.

1. Phonocardiograms recorded in cases of total A-V block, including cases of auricular flutter, show the occurrence of a sound whenever there is an auricular contraction; this auricular sound has usually two components distinctly separated one from the other by a short interval.

2. The auricular sound, as shown phonocardiographically, occurs not only during ventricular diastole, but also during ventricular systole, the vibrations being larger in the latter case.

3. The beginning and the first group of vibrations belonging to the auricular sound correspond to the auricular systole and are probably due to the increased tension of the auricular wall and to the compression exerted on the blood contained in the auricular cavity. The fact that the second group of vibrations corresponding to the auricular sound occurs after the auricular systole, suggests an extra-auricular origin; it may be ascribed to ventricular distention, to a change of position, to valvular distention, or to a resonance phenomenon.

4. When the auricular sound proper occurs synchronically with either the first or the second sound, the sound concerned is considerably reinforced. If it occurs during the short silence in the vicinity of either one of the ventricular sounds, it may resemble a reduplication of any of them. If it occurs early during diastole (isometric relaxation or ventricular inflow phases), a sound appears corresponding to the final moments of the ventricular inflow phase, similar in its mechanism of production to a summation gallop sound.

Blackman, S. S., Jr.: Syphilis of the Mitral Valve and Membranous Interventricular Septum of the Heart, Bull. John Hopkins Hosp. **58:** 111, 1935.

Two examples of syphilis of the mitral valve and membranous interventricular septum are described, occurring together with aortic insufficiency and typical syphilitic lesions of the aortic valve and aorta.

The lesions in the membranous septum and mitral valve are directly continuous with the syphilitic changes in the root of the aorta and aortic valves. The body of the anterior segment of the mitral valve is therefore chiefly affected, and the posterior mitral leaflet is relatively unaltered.

The gross lesions consist of diffuse leathery thickening of the membranous septum and great anterior mitral leaf. The left ventricular surface of the affected mitral segment and septum may show wrinkling and puckering resembling typical gross syphilitic lesions of the aorta. The mitral chordae tendineae are slightly affected.

Microscopically, gummatous necroses or dense vascular scars with perivascular round cell inflammation, or both, are found in the middle layers of the membranous

septum and the mitral valve. These lesions, continuous with the syphilitic lesions in the media of the aorta, are overlaid by strata of scar tissue formed especially on the left ventricular surface of the valve and septum. Scars and perivascular inflammation are found in the wall of the left auricle and in the muscular interventricular septum near the insertion of the syphilitic mitral valve and membranous septum.

Mitral lesions were suspected clinically in both of the cases described. Each case was characterized by the presence of persistent cardiac decompensation which could not be relieved, lasting for five and a half months in one case of extreme aortic insufficiency, and for a year and a half in the other, in which the aortic valve was moderately insufficient. The anatomical changes in the mitral valve in each case suggested some degree of insufficiency, and it is probable that the mitral lesions were in part responsible for the degree and persistent character of the cardiac decompensation.

Clements, A. B.: Isolated Tricuspid Stenosis of Probable Rheumatic Origin, Am. J. M. Sc. **190:** 389, 1935.

The case of tricuspid stenosis reported presents the following noteworthy features:

1. The extreme degree of narrowing of the tricuspid ostium, resulting in a valve grossly resembling a malformation rather than the end-result of an inflammatory process.
2. The absence of involvement of the other valves, except for a mitral insufficiency and slight sclerosis.
3. The absence of an etiological factor in the history, except for so-called minor rheumatic manifestations.
4. The finding of Aschoff bodies in the myocardium indicating the presence of rheumatic heart disease.
5. The indistinguishability clinically from mitral stenosis.
6. The absence of a pulsating liver and distention of the cervical veins.
7. The slight enlargement of the right auricle in face of the extreme stenosis.
8. The finding of advanced lesser circulation sclerosis, apparently an independent lesion.

Levin, E.: Forms of Hypervolemia in Cardiac Decompensation, Rev. argent. de cardiol. **2:** 17, 1935.

The condition of hypervolemia found in cardiac decompensation does not affect proportionally the blood corpuscles and the blood plasma. Either one of these elements may be predominantly affected, and there can also be mixed forms. The existing form is not simply a transient stage, but a well constituted form, inherent to the nature of the lesion which led to the cardiac insufficiency. Each hypervolemic variety shows a characteristic picture; intense dyspnea, mild cyanosis, and moderate mechanic edema, in cases of hyperplasmia, and the opposite picture in cases of corpuscular hypervolemia.

Book Reviews

ABNORMAL ARTERIAL TENSION. By Edward J. Stieglitz, M.D., New York, 1935, National Medical Book Co., 261 pages with 66 figures.

This volume is similar to one published by Stieglitz five years ago, with the addition of more recent data. It is a coherent account of arterial hypertension and reflects the strong personal views of the author. The book contains much information that is of value in the management and understanding of patients suffering from hypertension or hypotension and will well repay the practitioner who is willing to take the time to read it critically.

Many opinions are expressed as fact perhaps without sufficient regard to evidence to the contrary. For example, bismuth subnitrate is recommended categorically, and literature references are given only to papers of the author, who originated the treatment. Charts are presented which indicate a marked fall in arterial pressure on its administration, but no control period before treatment is shown. Other observers have not been convinced of the value of this treatment, and their views might well have been mentioned.

No attempt has been made to include the original, or indeed in many cases the most important, literature references. Whether this is justified or not, it leads to curious allocation of credit. Quite unconsciously it has also led the author to undue citation of his own publications. For example, much had appeared in the literature on the amyl nitrite test before Stieglitz's publication in 1930.

The theories offered as to the genesis of hypertension are interesting and thought-provoking but cannot be generally accepted as satisfying. It is possible that irritation leads to spasticity, to hypertrophy, to more spasticity, to muscular fatigue, to muscular hyperirritability, to more spasticity and so on, but the proof of it is neither given nor discussed. Stieglitz presents theories in such an enthusiastic and convincing manner that the unwary are likely to accept them as fact. In another edition of his book he might perform an invaluable service by indicating, in marginal notes, problems which are worthy of careful clinical study to prove or disprove his contentions.

In many places in the book he is admirably exact in his statements, but in others he lapses into obscurities which might easily be clarified. The value of the book to the practitioner might be enhanced by more detailed discussion of a number of statements of fact. Thus he states, "A severe proteinuria raises the specific gravity of urine, and it is important that the specimens be at or about 21°C. when examined." It might have been helpful to state how correction is made for the proteinuria to ascertain the nonprotein specific gravity. Again he states in reference to urea and creatinine clearance tests, "The interpretation of the results is not always clear," which may mean almost anything. Dosage of drugs are not given in many cases.

Stieglitz has a low opinion of surgical procedures designed to alleviate and to clarify the mechanism of hypertension. He dismisses them in two and one-half pages. Time alone will tell whether he is correct as regards therapeutic value, but their contribution to knowlege of the mechanism of hypertension should not be underrated.

While there are many suggestions and criticisms a reviewer might make, work by Stieglitz is always welcome as stimulating, interesting, highly individualistic, and thoroughly worth the time required for reading. He does not hesitate to say what he thinks, and a wholesome atmosphere will be created when others express their opinions equally whole heartedly.

I. H. P.

VIER VORLESUNGEN ÜBER KREISLAUFFRANGEN. By Doctor Bruno Kisch, Professor of Physiology at the University of Cologne. Paul Kuschbert, Köln, 1934.

This little volume of sixty-four pages contains four lectures by the author upon timely subjects relating to the physiology and pathology of the circulation, and based chiefly upon his own experimental work. The subjects of the lectures are: "Circulation and Metabolism," "Humoral Blood Changes in Circulatory Failure," "The Circulation and the Autonomic Nervous System," and "The Irradiation of Autonomic Reflexes."

L. A. C.